THE FAVORSKII REACTION OF THE PULEGONE OXIDES

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This is to certify that the

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ABSTRACT

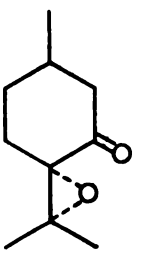
THE FAVORSKII REACTION OF THE PULEGONE OXIDES

by Phillip LeRoy Mattison

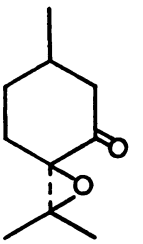
The Favorskii reaction of the two isomers of pulegone oxide is found to proceed stereospecifically and in good yield to give ring-contracted acids. Isomer I, m. 57°, upon treatment with sodium methoxide in glyme, gives cis- and trans-3-methylcyclopentane carboxylic acid, trans-pulegenic acid, and trans,trans puleganolic acid. Isomer II, m. 54°, gives cis- and trans-3-methylcyclopentane carboxylic acid, cis- and trans-pulegenic acid, trans,cis-puleganolic acid, and cis, trans-puleganolide. Cis,trans-puleganolide may arise via an epimerization of trans,cis-puleganolic acid, indicating that the rearrangement is stereospecific, but that the products may subsequently lose their stereochemical integrity.

The rearrangement is discussed in terms of a direct displacement of the epoxide oxygen by an α-anion, leading to a cyclopropanone intermediate. Opening of this intermediate occurs predominantly to give a tertiary anion beta to the hydroxyl group. Elimination of hydroxide ion then leads to pulegenic acid, and protonation results in puleganolic acid. This protonation is also stereospecific, and proceeds with

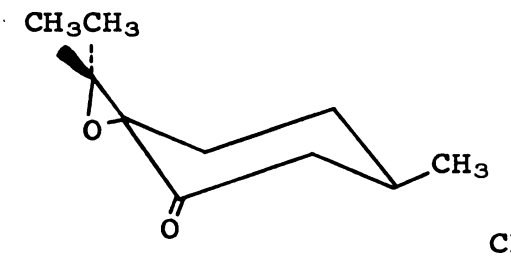
retention of configuration, a result consistent with previous studies of electrophilic carbanion substitution. These results reverse the previous assignment of pulegone oxide configurations.



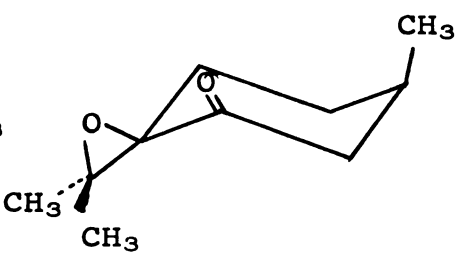
I



II



Ia



IIa

The conformations of I and II are discussed, and Ia and IIa appear to predominate at room temperature. Using 5α,6α- and 5β,6β-epoxycholestan-4-one as model compounds, the Cotton effects of spiro-epoxy ketones are found to be consistent with a normal application of the Octant Rule. The chemical shifts of the α-hydrogens of I and II are rationalized in terms of conformations Ia and IIa.

The recent literature of the Favorskii reaction is reviewed.

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By

Phillip LeRoy Mattison

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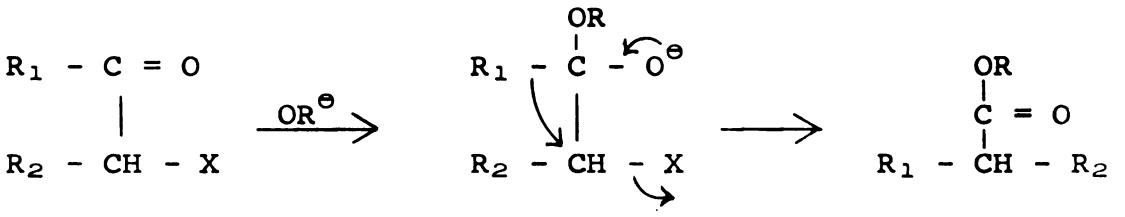
INTRODUCTION AND HISTORICAL BACKGROUND

During the evolution of the Favorskii reaction, several mechanisms have been proposed. Of these, three have retained prominence. A semi-benzylic mechanism (eq. 1) was put forth by Tchoubar (1) in 1939. According to this proposal, the α' carbon atom migrates to the α-carbon with the expulsion of halide.[1] On this basis, one would expect different acids

(1) 

to be derived from isomeric α-halo ketones.

However, in an elegant experiment, Loftfield (2) showed that this was not always the case. 2-Chlorocyclohexane (I), having C^{13} equally distributed between C_1 and C_2, gave an ester of cyclopentane carboxylic acid (II) when treated with alcoholic base (eq. 2). Degradation of II showed that 50% of the C^{13} was at the carboxylic carbon, 25% at C_1, and 25% at C_2 of the cyclopentane ring.

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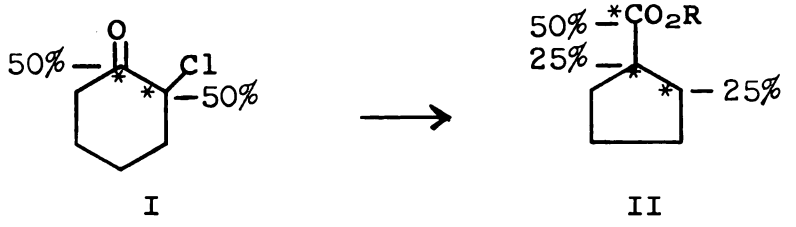
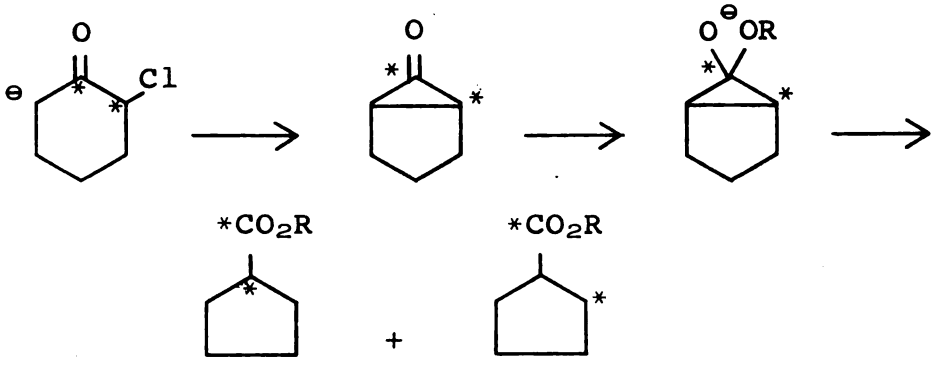
[1]Throughout this thesis, "α" shall designate the carbon atom bearing the leaving group; "α'" shall indicate the other carbon adjacent to the carbonyl.

(2) 

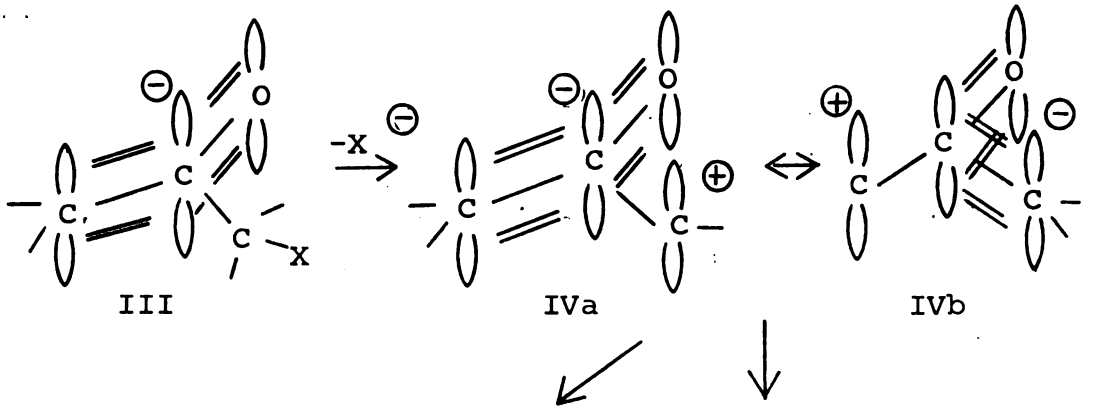
I II

Application of the semi-benzylic mechanism to this reaction would require the C^{13} to be equally distributed between C_1 and the carboxylic carbon. Loftfield proposed the formation of a cyclopropanone intermediate by intramolecular displacement of the halide by an enolate anion (eq. 3). Opening of the three membered ring in the corresponding hemiketal conjugate base would occur at both sides with equal probability, leading to the observed product mixture.

(3) 

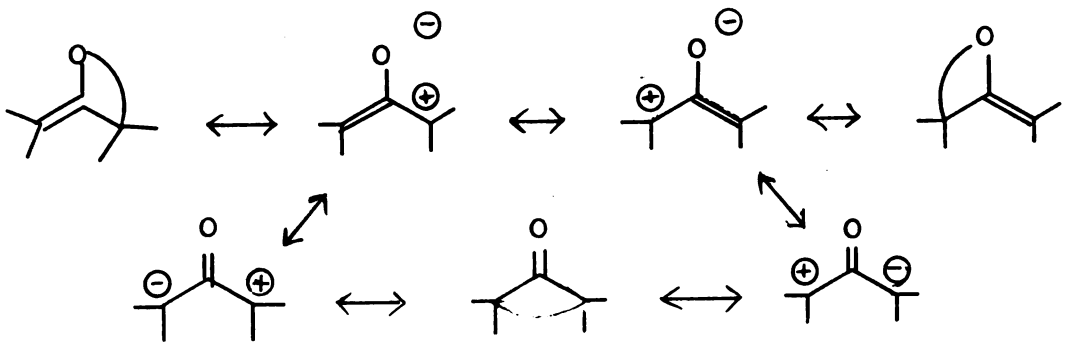
An alternate rationale, offered by Aston and Newkirk (3) and later supported by Burr and Dewar (4), involved the manner of formation of the cyclopropanone. Since the orbital occupied by the α'-anion must be parallel to the carbonyl π-bond (see III), it seemed sterically difficult for it to attain the necessary geometry for intramolecular expulsion of

halide. Instead, the enolate species (III) may spontaneously lose halide ion to form a zwitterionic species which would have two chief resonance contributors (IVa and b). From LCAO-MO calculations, Burr and Dewar predicted that the



reaction of III ⟶ IV should be accompanied by an increase in resonance energy of ca. 14 kcal/mole. They further predicted that collapse of the zwitterionic species to a cyclopropanone should be exothermic.

Fort (5) has commented that the zwitterionic species should lack stability, since all the resonance contributors have charge separation. To alleviate this alleged instability, he proposed a stabilization through π-bonding. It should be noted that in the "cyclopropanone" resonance contributor (IVc) the two α-carbons are π-bonded; formation of a σ-bond would involve rehybridization of the carbon orbitals and rotation



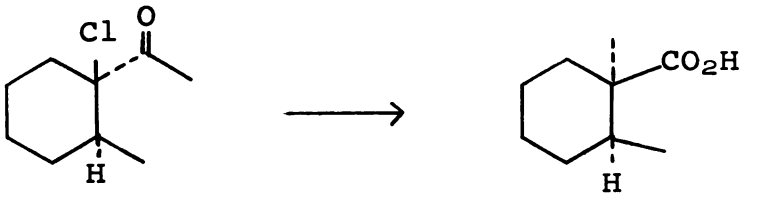
IVc

about the α-bonds. Thus, Loftfield's cyclopropanone is not merely a resonance contributor to the zwitterionic form.

It might be expected that the zwitterionic intermediate would be favored by a medium of high solvating power, while the Loftfield mechanism would be favored by non-polar solvents. If direct cyclopropanone formation occurs the products should be stereospecifically related to the configuration of the departing halide. On the other hand, one would not expect this stereospecificity to occur if the reaction proceeds via the zwitterionic intermediate, since it is planar and may collapse to either of two epimeric cyclopropanones.

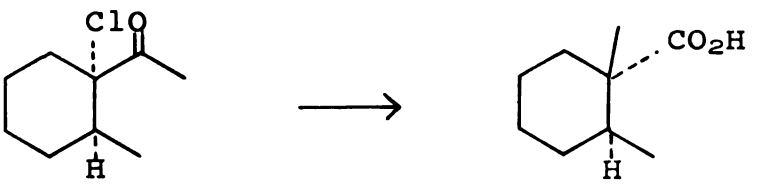
Stork and Borowitz (6) reported a stereospecific rearrangement of α-chloroketones Va and Vb in a non-polar solvent (eq. 4,5). Treatment of epimeric 1-chloro-2-methyl-1-acetylcyclohexanes (Va and b) with sodium benzyloxide in ether, followed by hydrogenolysis of the resulting esters, gave the acids (VIa and b) corresponding to inversion at the α-carbon atom.

(4)



Va VIa

(5)



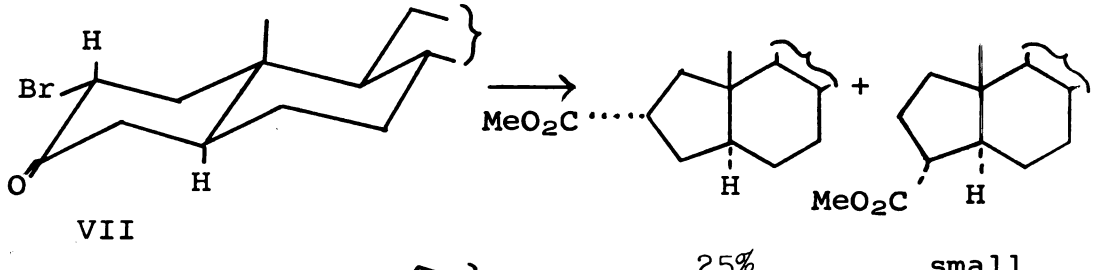
Vb VIb

House and Gilmore (7) observed the same stereospecificity when Vb was treated with sodium methoxide in dimethoxyethane, but obtained a 5:4 ratio of VIa:VIb when Vb was treated with sodium methoxide in methanol. Similarly, Tchoubar and co-workers (8), treating Vb with various bases in different polar solvents, found varying ratios of VIa and b in the product mixture.

The results in polar solvents are consistent with the formation of a planar zwitterionic intermediate which as it collapses to form cyclopropanones, may experience asymmetric induction, resulting in a stereoselective production of products. Furthermore, it is possible that polar solvents may effect an equilibrium between an already-formed cyclo-propanone and its zwitterion.

The Favorskii rearrangement has been applied to a variety of steroid substrates. When 2α-bromo-5α-cholestan-3-one(VII) was treated with sodium methoxide in a methanol-ether mixture, a 25% yield of methyl A-nor-5α-cholestane-2α-carboxylate plus a small amount of methyl A-nor-5α-cholestane-3α-carboxylate was obtained (9) (eq. 6) (Pappas and Nace (10) obtained similar products from 2α-bromo-5α-progestan-3,20-dione). Using anhydrous ether as a solvent, approximately equal amounts of the 2α- and 3α-methyl esters were found. Treatment of 4β-bromo-5β-cholestan-3-one (VIII) with sodium methoxide in methanol-ether gave methyl A-nor-5β-cholestane-2β-carboxylate and methyl A-nor-5β-cholestane-3β-carboxylate, each in 24% yield (eq. 7). All of these products (from VII and VIII) are those predicted on the basis of a stereospecific formation of a cyclopropanone intermediate. It should also be noted that in each case the departing halide is equatorial, a situation

(6)

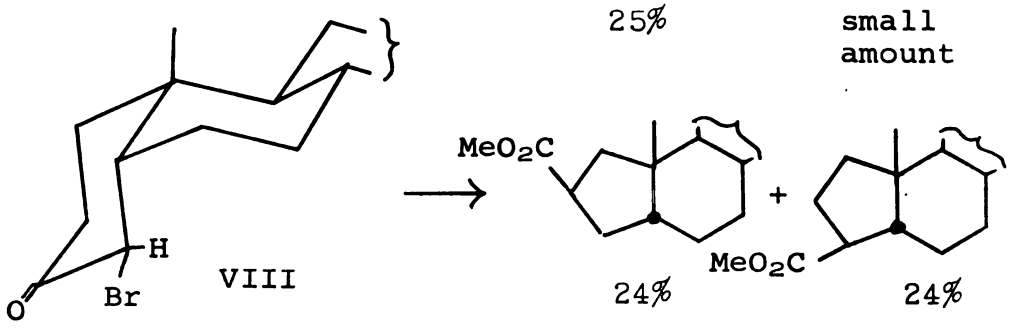


VII

25%

small amount

(7)



VIII

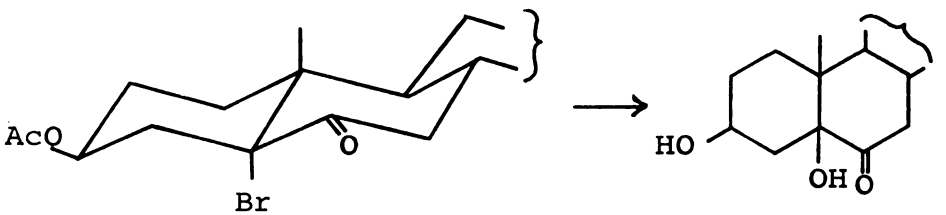
24%

24%

that should be optimal for a stereospecific Favorskii reaction.

The reaction of 5α-bromocholestan-3β-ol-6-one (**IX**) with sodium ethoxide in ethanol (11) gave a 36% yield of cholestan-3β,5β-diol-6-one (**X**) instead of B-ring contraction (eq. 8). While a number of different explanations for the observed

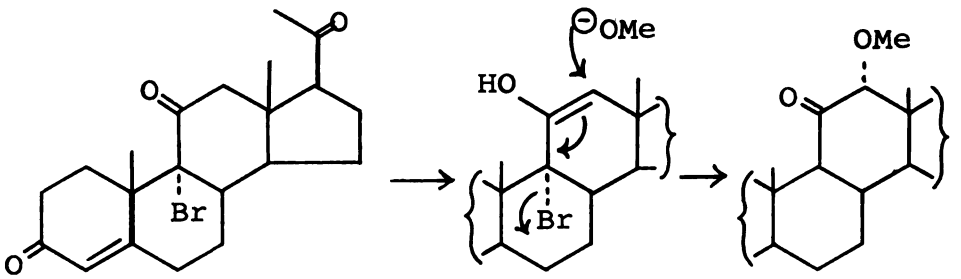
(8)



IX **X**

product have been offered (11,6), the fact that the α-halogen is axial appears to be significant. As long as the cyclohexane ring remains in a chair conformation, displacement of an axial α-substituent by an α'-anion would be expected to be difficult. Further, examples of this phenomenon are found in the reaction of 9α-bromopregn-4-ene-3,11,20-trione (**XI**) with sodium methoxide in methanol, yielding 12α-methoxypregn-4-ene-3,11,20-trione (**XII**) (12) (eq. 9), and in similar transformations with other pregnane and ergostane systems (13). Again, the axial bromine cannot be easily displaced by the C_{12}-anion, and a mechanism involving SN_2' attack by methoxide on the enol (partial structure **XIII**) has been suggested (13).

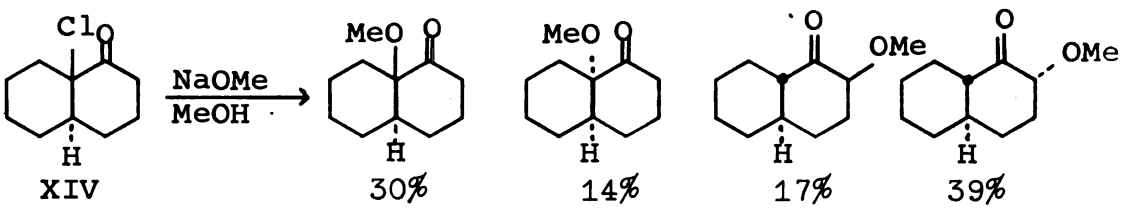
(9)



XI XIII XII

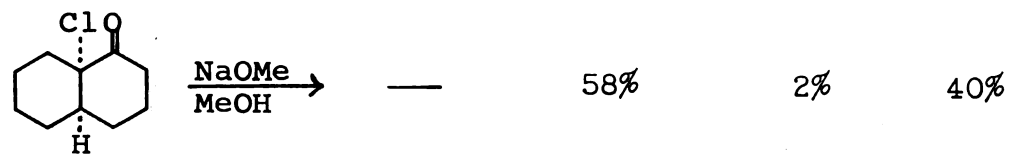
House and co-workers (14,15) have studied the reactions of the trans- and cis-9-chloro-1-decalones (XIV and XV, respectively) with methoxide ion in two solvents. The exclusive formation of solvolysis products in methanol (eq. 10, 11) suggests a zwitterionic intermediate; however, the same

(10)



XIV 30% 14% 17% 39%

(11)

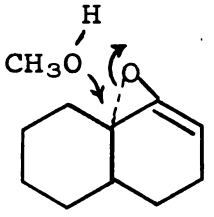


— 58% 2% 40%

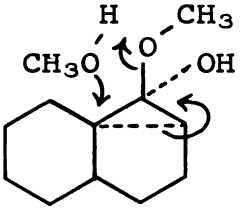
XV

intermediate should be formed from both XIV and XV, leading to identical product ratios from these isomers. The fact that different product ratios are found indicates that some other mechanism is in operation. Explanations of these

results (15) have included the formation of an alkylidene epoxide (XVI), or an abnormal reaction of a cyclopropanone hemiketal (XVII). These rationalizations do not overcome all objections, and must be regarded as tenuous.

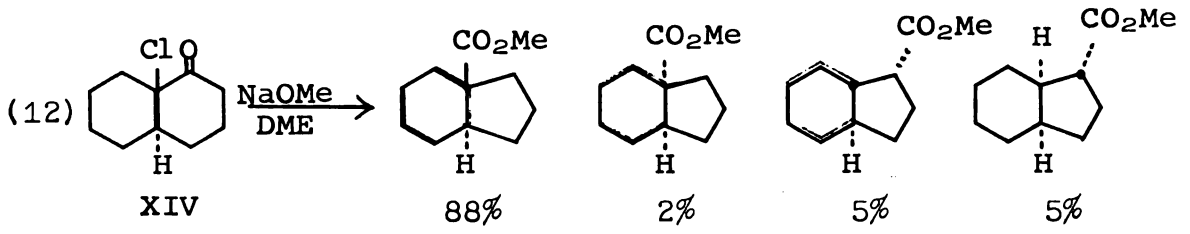


XVI

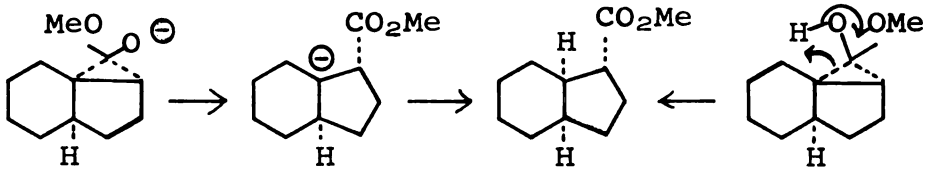


XVII

The Favorskii reactions of XIV and XV were also studied in dimethoxyethane (DME) (15), and were found to give only ring contracted esters in a predominantly stereospecific rearrangement (eq. 12,13). This is a surprising result in view of the fact that the trans-chlorodecalone (XIV) possesses a chloride which is rigidly held in an axial position. However, examination of models shows that a twist-boat conformation of the ketone ring permits the α'-anion to effect a rear side displacement of chloride ion.

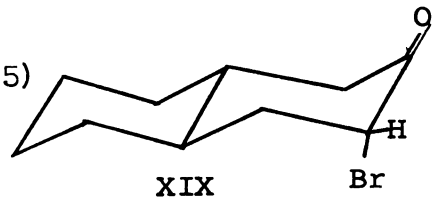


The predominant formation of the all-cis methyl hydrindane-1-carboxylate (XVI) from XV is of interest, since it represents an abnormal opening of the cyclopropanone ring (see XVII) to give a tertiary, rather than a secondary anion. This anion must then be stereospecifically protonated to give the cis ring system (eq. 14). Alternatively, a discrete carbanion may not be formed at all, but rather proton transfer may occur as the cyclopropanone hemiketal (XVIII) is opened. The latter explanation seems more reasonable.

(14) 

XVII XVI XVIII

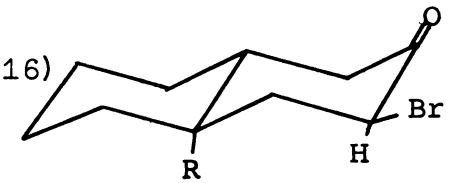
Another α-halodecalone system has been studied recently by Smissman and co-workers (16). Treatment of 3-a-bromo-trans-2-decalone (XIX) with sodium ethoxide in either ethanol or DME gave no Favorskii acids. Only solvolysis products and a ring-opened diacid were formed (eq. 15). The isomer having an equatorial halide, 3-e-bromo-trans-2-decalone (XXa, R=H), also gave solvolysis products plus a 13% yield of a hydrindane carboxylic acid (XXIA, R=H) when treated under the same conditions (eq. 16). Deuterium incorporation studies with XX showed rapid exchange at the α-carbon, implying an epimerization of the α-bromide. It was suggested that the presence

(15) 

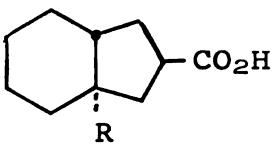
XIX

NaOEt
EtOH
or DME

Solvolysis Products

(16) 

NaOEt
EtOH
or DME

Solvolysis Products + 

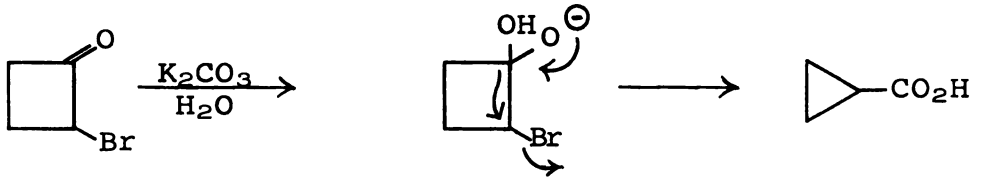
XXa, R = H
XXb, R = CH_3

XXIa, R = H
XXIb, R = CH_3

of axial halide was responsible for the low yield of XXIa. Accordingly, 2-e-bromo-9-methyl-trans-3-decalone (XXb, R=CH_3) was synthesized with the expectation that the added axial methyl group would hinder the formation of the axial bromide, and thus lead to increased yields of Favorskii products. Indeed, under the same conditions, XXb gave ca. 40% yields of XXIb. Smissman concluded that in this system the Favorskii reactions proceed by intramolecular displacement of halide to give a cyclopropanone. If the zwitterion could also lead to Favorskii products, these would have been expected from the axial isomer also.

Favorskii-like reactions have been observed with α-halo ketones having no α'-hydrogen. This type of reaction has been separately classed as the Quasi-Favorskii reaction, and requires a pseudo-benzylic mechanism.

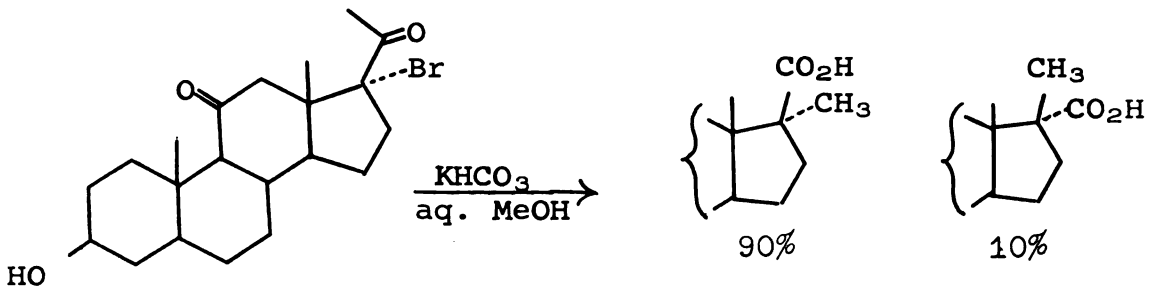
2-Bromocyclobutanone has been observed to give cyclopropane carboxylic acid derivatives under Favorskii conditions (eq. 17). The mechanism has been shown to be of the semi-benzylic type by means of stereochemical, kinetic, and deuterium incorporation studies (17). That a cyclopropanone intermediate is not formed is not surprising in view of the strain inherent in the requisite [1.1.0] ring system.

(17) 

The Favorskii reaction has also been used in the synthesis of cubane (18,19). Due to the geometry of this system, it is probable that this reaction also proceeds by a semi-benzylic mechanism.

The Favorskii reaction of 17α-bromo-5α-pregnan-3β-ol-11,20-dione (**XXII**) has been extensively studied (20-23). A stereospecific rearrangement would be expected to give 17β-methyl-5α-pregnan-3β-ol-11-one-17α-carboxylic acid (**XXIV**); however, the 17α-methyl isomer (**XXIII**) is found to predominate (eq. 18). In the most recent study of this reaction, Deghenghi et al. (23) examined the incorporation of solvent deuterium in the products. A single deuterium was found in both **XXIII** and **XXIV**; undeuterated and polydeuterated species were absent. It may be concluded from this that no exchange occurs prior to rearrangement. Furthermore, a semi-benzylic mechanism can be eliminated, since specific monodeuterium incorporation cannot

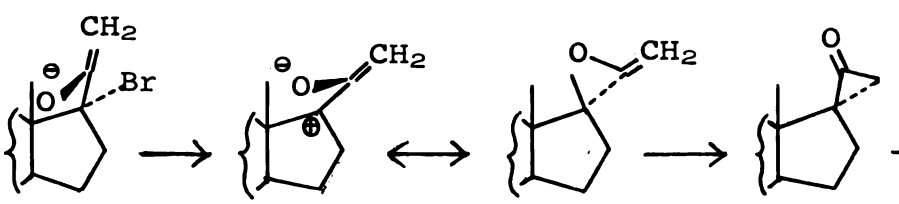
(18)



XXII XXIII XXIV

be accommodated by this pathway. The authors favor a modified cyclopropanone formation in rationalizing their results. In the first step of this mechanism (eq. 19) an enolate anion is formed; rotation about the C_{17}-C_{20} bond places the enolate oxygen in a position away from the bromine, thus relieving

(19)

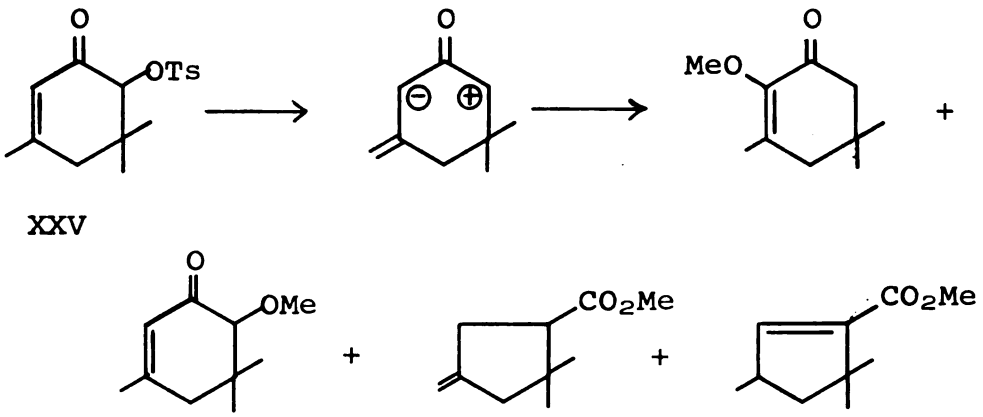


XXIII

dipole-dipole interaction. Loss of halide then occurs, with electrostatic attraction (or a type of π-bonding) maintaining the geometry of the system. This intermediate, which may have resonance contributors of the type mentioned earlier, collapses to form a cyclopropanone which reacts further to yield XXIII.

Fort (24) has reported that the 6-tosylate of isophorone (XXIV) reacts with sodium methoxide in methanol to give products which are readily explained by a zwitterionic Favorskii intermediate (eq. 20).

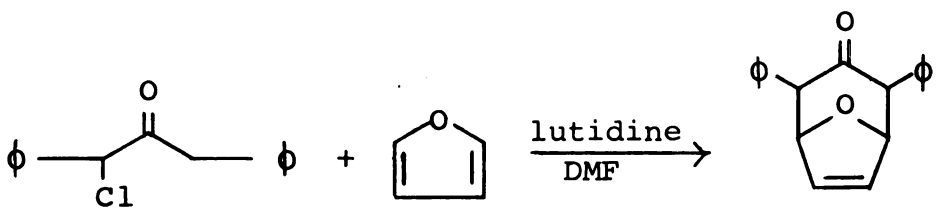
(20)



XXV

In addition, Fort (25) has demonstrated that treatment of α-chlorodibenzyl ketone (XXVI) with 2,6-lutidine and furan in dimethyl formamide (DMF) solution gives an 18% yield of a bicyclic product (eq. 21). A dipolar intermediate was again used to explain these results.

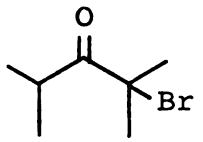
(21)



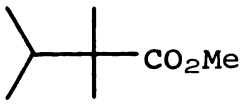
XXVI XXVII

Recently, Turro has been able to isolate and characterize a series of cyclopropanones (26-28). 2,2,3,3-Tetramethylcyclopropanone (XXVIII) reacted with sodium methoxide in methanol or DME to give a 97% yield of methyl 2,2,3-trimethylbutyrate (XXIX), and a 3% yield of tetramethylmethoxyacetone (XXX) (26) (eq. 23). This was the first direct evidence that a cyclopropanone reacts with basic nucleophiles to give Favorskii products. Although the same cyclopropanone could in principle be formed from tetramethylbromoacetone (XXXI),

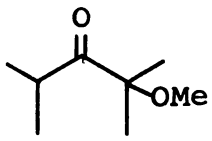
reaction of XXXI with sodium methoxide gave primarily XXX (eq. 22).

(22)  XXXI

NaOMe, ether

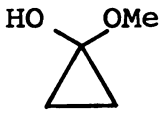
 XXIX' 12%

+

 XXX 88%

(23)  XXVIII

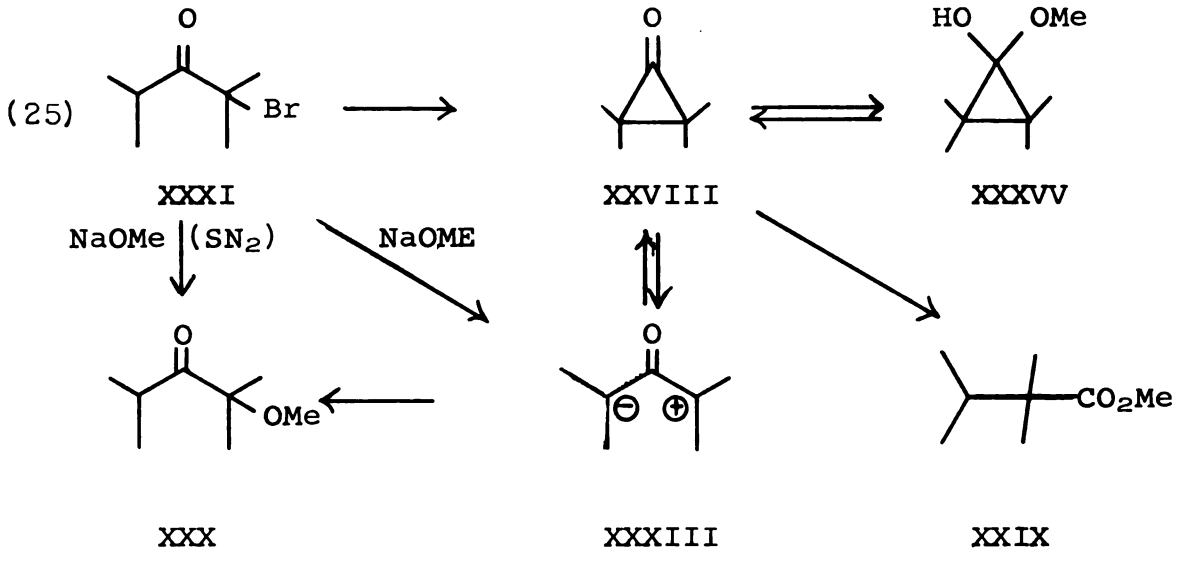
NaOMe, MeOH or DME → 97% 3%

 XXXII

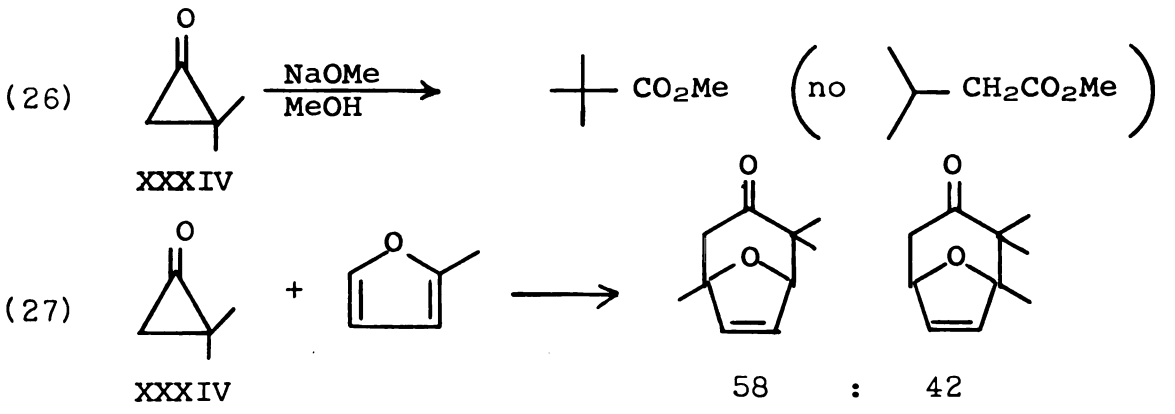
NaOMe, MeOH or DME → 98% < 1%

(24) XXXII → (MeOH) 24% 76%

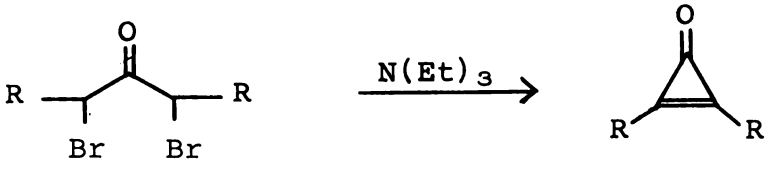
It may therefore be concluded that the reaction of XXXI → XXX occurs mainly by simple displacement by methoxide or via a zwitterionic intermediate; only a small amount may be converted to the cyclopropanone XXVIII. The formation of large amounts of XXX from the reaction of the hemiketal (XXXII) with methanol (eq. 24) suggested that in a polar solvent the cyclopropanone is in equilibrium with the more reactive zwitterion (XXXIII) (see eq. 25).



Treatment of 2,2-dimethylcyclopropanone (XXXIV) with methanolic sodium methoxide gave a > 70% yield of methyl 2,2-dimethylpropionate (27) (eq. 26). No methyl 3-methylbutanoate was found. Opening of the cyclopropanone ring thus occurs at the least substituted α-carbon as predicted by previous mechanistic interpretations of the Favorskii reaction (29). XXXIV was also observed to react with 2-methylfuran to give an isomeric mixture of 1:1 adducts (eq. 27); the intermediacy of a zwitterionic species analogous to that proposed by Fort (25) seems doubtful in this case.

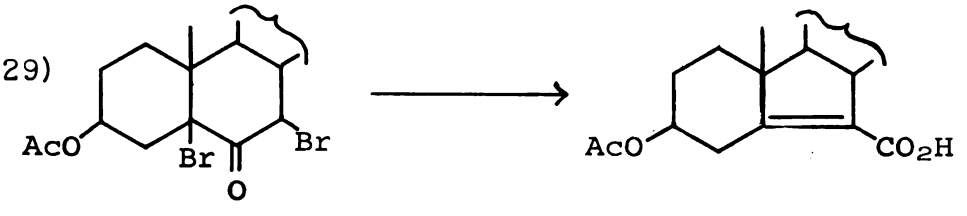


Base initiated cyclization of α,α'-dihaloketones has been used with success in the preparation of cyclopropenones (eq. 28). Yields of 12 to 60% have been reported for the cases where R = propyl (30), phenyl (31), butyl, and cyclo-C_5H_{10} (32).

(28) 

These reactions proceed through the dehydrohalogenation of an α-bromocyclopropanone. The base used must be a poor nucleophile in order to avoid opening the ring, since hydroxide and alkoxide result in the formation of acrylic acid derivatives.

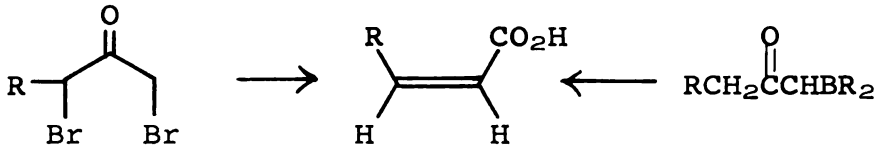
Favorskii reactions of ketones having more than one α-halogen have been studied extensively. Woodward and Clifford (33) found that treatment of the acetate of 5,7-dibromocholestan-3β-ol-6-one (XXXV) with anhydrous pyridine, followed by aqueous hydrolysis, gave the acetate of B-norcholest-5-en-3β-ol-6-carboxylic acid (XXXVI) (eq. 29). This reaction has

(29) 

XXXV XXXVI

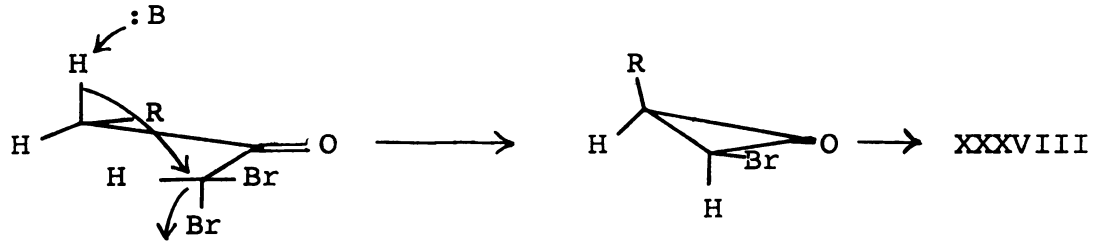
also been successfully applied to the ring-contraction of cyclic dibromoketones having eight (34), and twelve (35) membered rings. Acyclic dihalo ketones have also been studied, and reveal an interesting geometric specificity in the product. Treatment of 1,3-dibromobutanone (XXXVII) with aqueous bicarbonate gave a 77% yield of isocrotonic acid (XXXVIIIa)(36) (eq. 30). With stronger bases (K_2CO_3, KOH) the specificity was retained, but yields were lower. α,α-Dihalo ketones of type XXXIX (R = ethyl, n-propyl, and n-pentyl) also gave substituted cis-acrylic acid derivatives in ca. 75% yields (37).

(30)

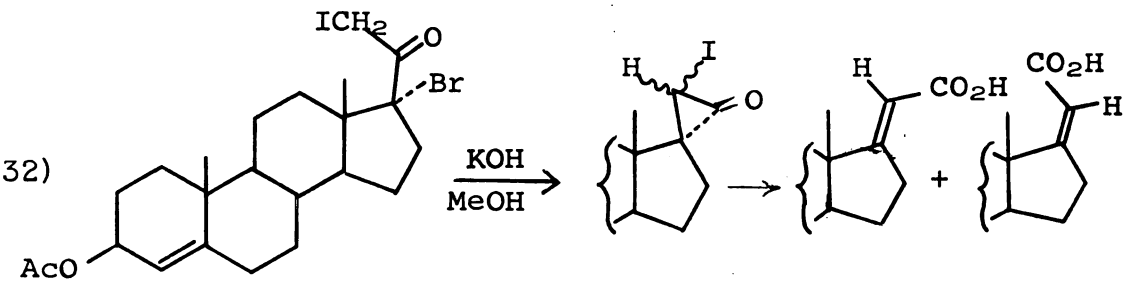


XXXVII XXXVIII (a, R=CH_3) XXXIX

These results suggest a concerted formation and cleavage of cyclopropanone intermediates (eq. 31). An α'-anion displaces bromide in such a manner as to give a cyclopropanone having the alkyl substituent cis to the remaining halide. Basic cleavage then occurs with immediate loss of halide; if a discrete anion were formed it would have time to rotate and subsequently produce a cis-trans mixture of acrylic acid derivatives. In addition, a discrete anion should be formed at the halogen-bearing carbon.

(31) 

The iodobromoketone XL, upon treatment with methanolic potassium hydroxide, has been found to give a 70% yield of a mixture of conjugated acids (38) (eq. 32). In this case,

(32) 

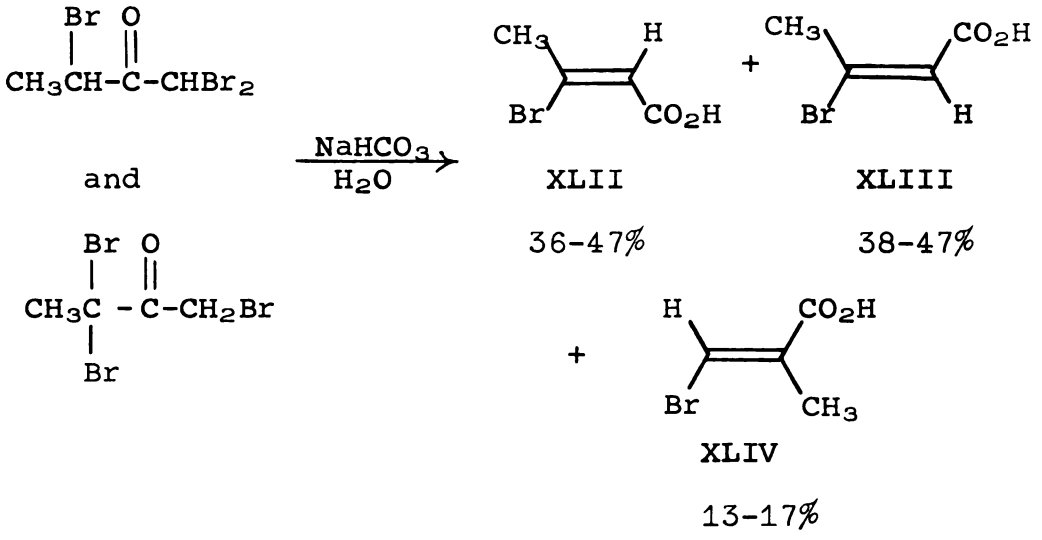
XL XLI

formation of an iodocyclopropanone is followed by collapse with loss of iodide ion to the observed products. If this collapse is assumed to be stereospecific, then the stereochemistry of the products is determined in the formation of the 3-membered ring intermediate. Thus, attack by either of two epimeric C_{21}-anions will lead to epimeric iodocyclopropanones (XLI), followed by stereospecific collapse of each to give the observed mixture.

Trihaloketones have been investigated by Rappe and coworkers. 1,1,3-Tribromobutanone and 1,3,3-tribromobutanone were observed to give similar ratios of acidic products

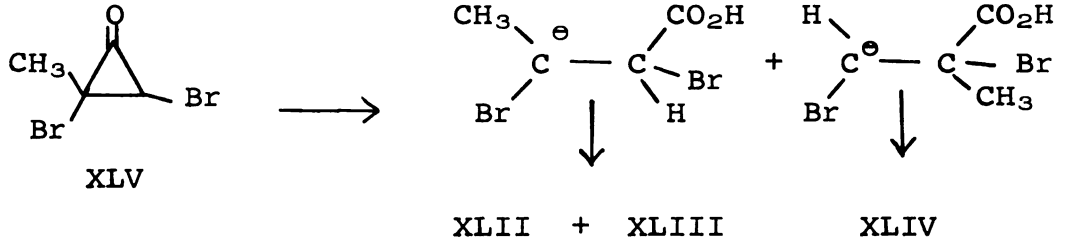
(XLII-XLIV) (39,40) (eq. 33). This would indicate that both

(33)



reactions proceed through a common intermediate which is probably 2,3-dibromo-2-methylcyclopropanone (XLV). Rappe (41) suggested that XLV is opened in a non-concerted process to give a formal anionic species, which could rotate before eliminating bromide ion, and thus yield a mixture of geometric isomers (eq. 34). However, no explanation was given as to

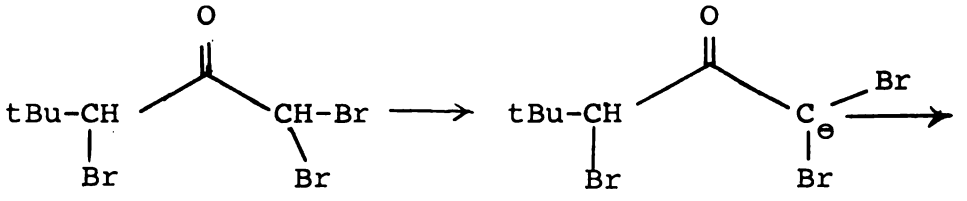
(34)



why a secondary anion should predominate over a primary in this system.

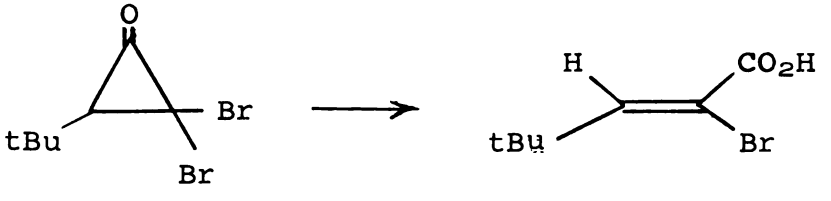
Somewhat surprisingly, 1,1,3-tribromo-4,4-dimethyl-2-pentanone (XLVI), upon treatment with bicarbonate, gave only one acid, trans-2-bromo-4,4-dimethyl-2-pentenoic acid

(XLVII) (42) (eq. 35). Semibenzylic and ketocarbene mechanisms were discounted, since these would lead to more than one acid.



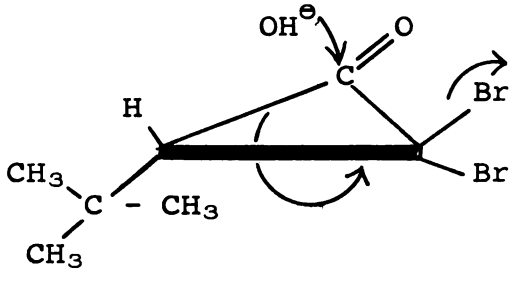
XLVI

(35)

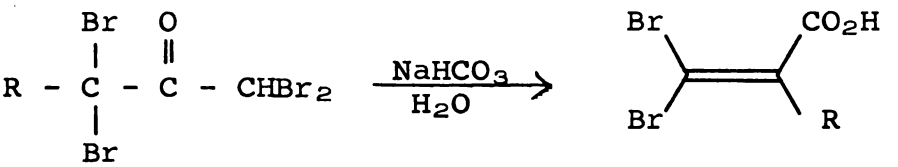


XLVII

In the cyclopropanone mechanism which was put forth, an anion at C_1 is formed and displaces the C_3-bromine. This specificity may be due either to the inaccessibility of the C_3-proton, or to a relatively fast reaction of the C_1-anion, since this would relieve steric crowding at C_3. The manner of opening of the intermediate is interesting, since it requires a stereospecific flow of electrons.



Dehmlow has applied the Favorskii reaction to 1,1,3,3-tetrachloroacetone (43). Treatment with aqueous bicarbonate gave 2,2-dichloroacrylic acid but none of the 1,2-isomer. Rappe (44) observed similar results with the tetrabromo compound (XLVIII, R=H) and has extended the method to include the analogs where R = methyl, ethyl, propyl, and isopropyl.

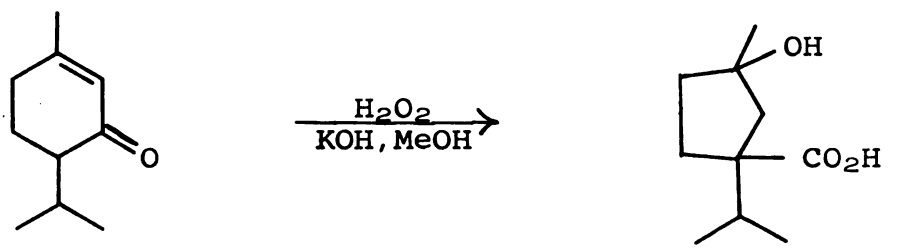
(36) 

XLVIII XLIX

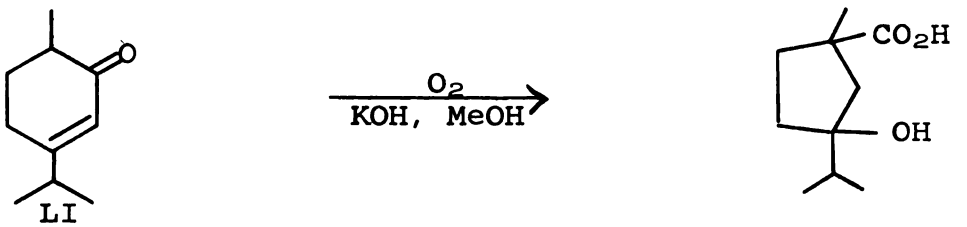
33-79%

With the three higher analogs, a 10-15% yield of the 2,3-dibromo-2-alkenoic acids is also obtained.

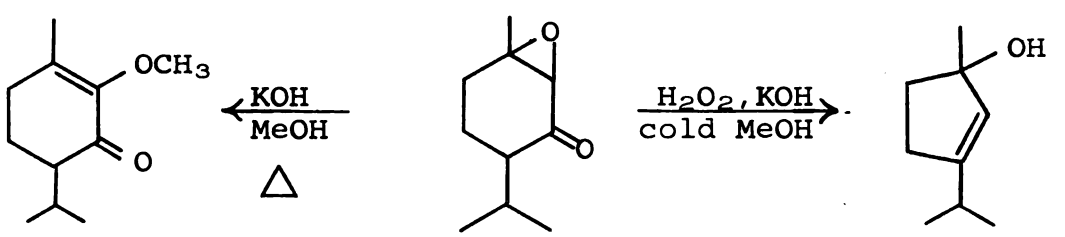
Several Favorskii reactions have been reported for substrates having an epoxide oxygen as the leaving group. In a study of the reaction of α,β-unsaturated ketones with alkaline hydrogen peroxide, Treibs (45) found that piperitone (L) gave a hydroxy acid in ca. 40% yield (eq. 37). Similarly, carvenone (LI) gave an isomeric hydroxy acid (46) (eq. 38). By using milder conditions, Treibs was able to isolate the

(37) 

L

(38) 

epoxy ketone intermediates. Under basic reaction conditions, these epoxy ketones were also converted to the same hydroxy acids. By varying the reaction conditions, other products were obtained. Thus, the slow addition of methanolic potassium hydroxide to a refluxing methanol solution of piperitone oxide (LII) gave a diosphenol methyl ether, while reaction with hydrogen peroxide and potassium hydroxide in cold methanol gave an unsaturated tertiary alcohol (47) (eq. 39).

(39) 

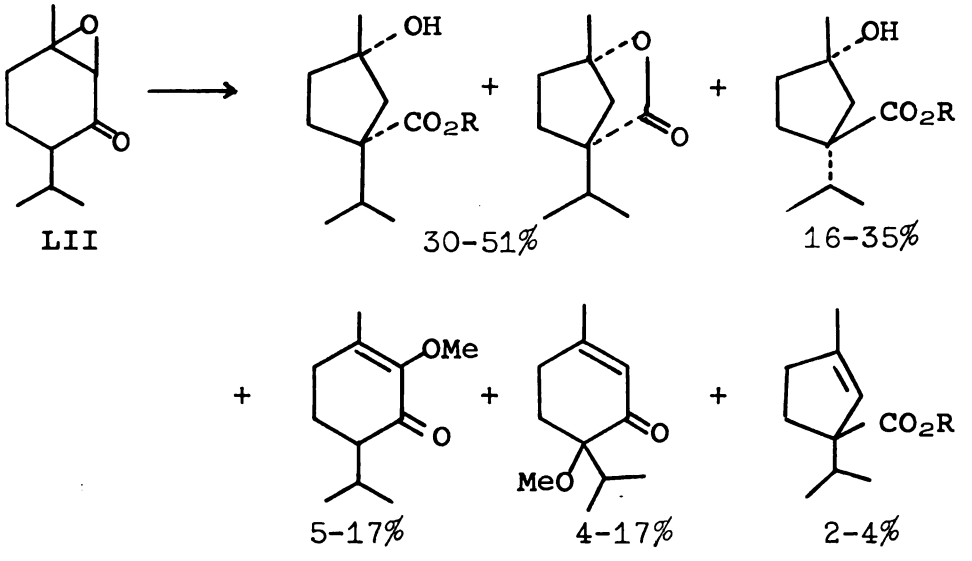
LII

Treibs (48) also investigated the reactions of several other α,β-epoxy ketones with potassium hydroxide in refluxing methanol. The products in most cases were diosphenols and diosphenol methyl ethers. With pulegone oxide, an unidentified mixture of acids was obtained.

House and Gilmore reinvestigated the reactions of piperitone oxide and isophorone oxide with base (49). Using methanolic sodium hydroxide or sodium methoxide, piperitone

oxide gave a mixture of ring-contracted acids and solvolysis products (eq. 40). The lack of stereospecificity in the

(40)

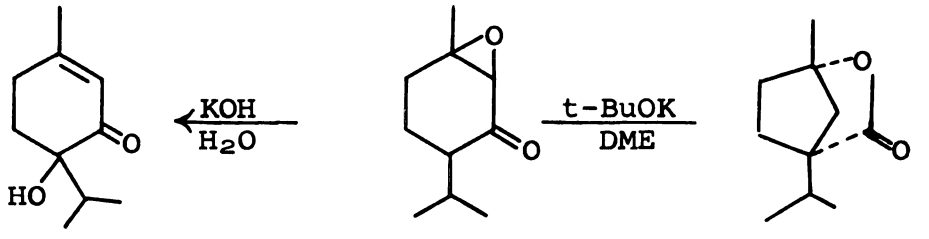


LII 30-51% 16-35%

5-17% 4-17% 2-4%

formation of the acids, as well as the solvolysis products, was rationalized on the basis of a zwitterionic intermediate. When the reaction was run in aqueous potassium hydroxide, the hydroxy piperitone (LIII) was formed in 88% yield as the only neutral product (eq. 41). Treatment of LII with potassium tert-butoxide in DME gave the cis-lactone in 70% yield. The stereospecificity of this latter case argues against a zwitterionic intermediate.

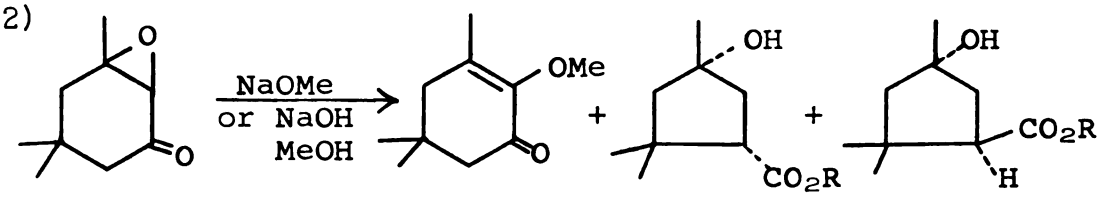
(41)



LIII LII

Similar reactions with isophorone oxide (LIV) gave predominantly solvolysis products (eq. 42). The trace of ring-contracted acid formed was a mixture of stereoisomers. Again, these results are consistent with the intermediacy of a zwitterionic species.

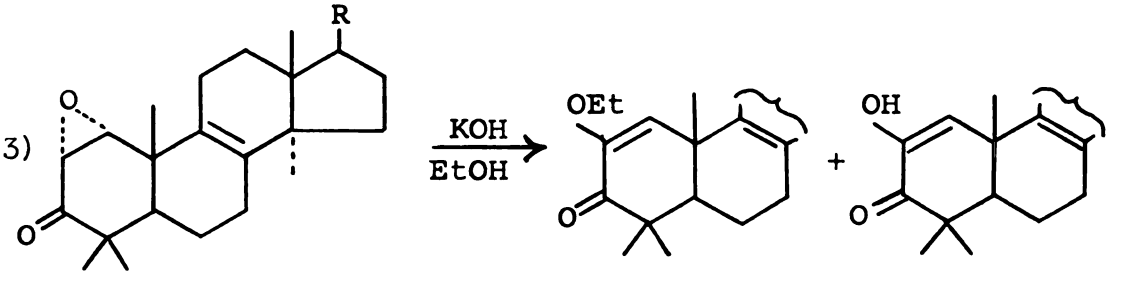
(42)



LIV 81-85% 0-3% 0-3%

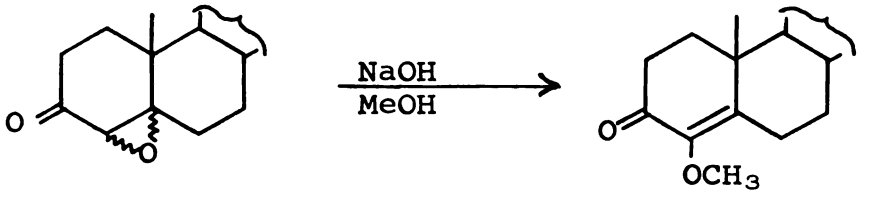
Treatment of 1α,2α-epoxylanost-8-en-3-one with ethanolic potassium hydroxide gave only solvolysis products (50) (eq. 43). Similar results attended the methoxide ion initiated reaction of 1α,2α-epoxy-5α-cholestan-3-one (51).

(43)



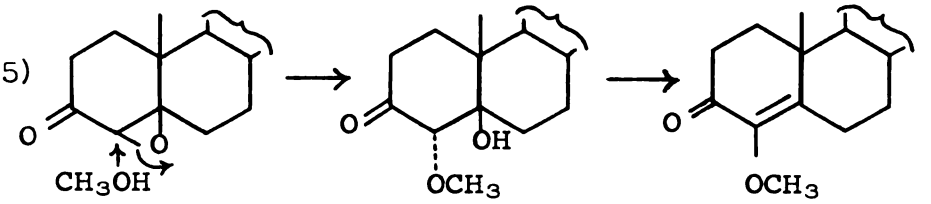
Reusch and LeMahieu (52) have also observed that both 4β,5β- and 4α,5α-epoxycholestan-3-one react with methanolic sodium hydroxide to give 3-methoxycholest-4-en-3-one (eq. 44).

(44)



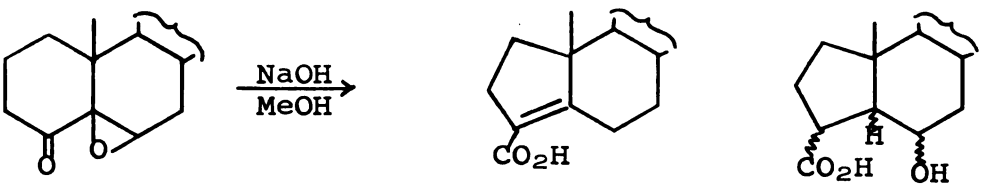
These solvolytic reactions are believed to proceed via a direct nucleophilic displacement of the epoxide oxygen at the α-carbon (eq. 45). Subsequent basic elimination of hydroxide ion would lead to the observed products.

(45)



One would expect that in an epoxy ketone having a tertiary α-carbon, the tendency toward simple displacement would be reduced. Furthermore, since such a substrate has no α-hydrogen, the final elimination could not occur. In this regard, LeMahieu (51) has examined the reaction of 5β,6β-epoxycholestan-4-one (LV) in methanolic sodium hydroxide. The observed products were A-norcholest-3-en-3-carboxylic acid (LVI) and A-nor-5ξ-cholestan-6ξ-ol-3ξ-carboxylic acid (LVII) (eq. 46). While the stereochemistry of the latter product was not rigorously established, it probably arises from an abnormal opening of a cyclopropanone intermediate to give a tertiary, rather than a secondary anion.

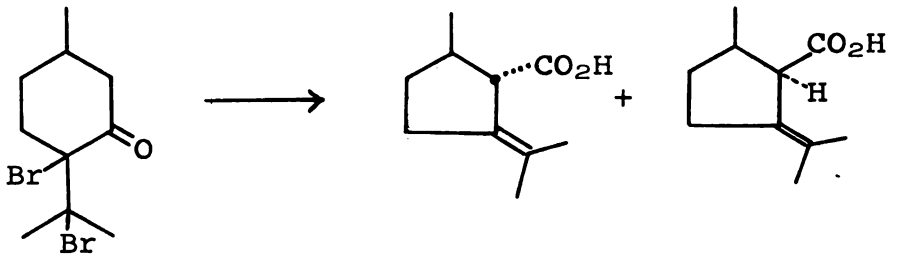
(46)



LV LVI LVII

Cavill and Achmad (53) have investigated the Favorskii reaction of pulegone dibromide and pulegone oxide. Reaction

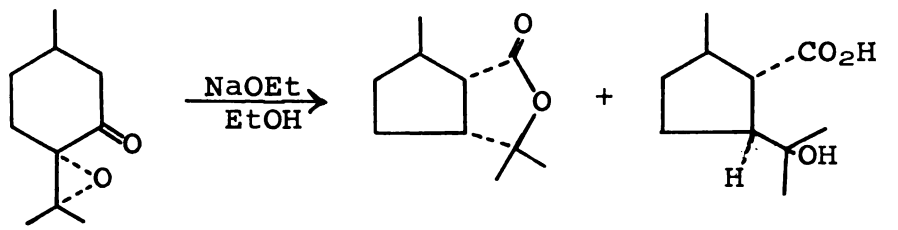
of the dibromide with ethanolic sodium ethoxide gave only trans-pulegenic acid, whereas aqueous potassium hydroxide gave a 40:60 mixture of trans- and cis-pulegenic acids, respectively (eq. 47). These results were interpreted in terms of stereospecific formation and reaction of a

(47) 

cyclopropanone intermediate in ethanol as a solvent, and formation of a zwitterionic intermediate in the aqueous system. The authors proposed that the dibromide was composed essentially of one isomer; however, Wolinsky (54,55) asserts that the dibromide is rather a mixture of isomers, both of which react stereospecifically. The ethyl esters which are formed in absolute ethanol are rapidly isomerized, and are hydrolyzed to acids at different rates, resulting in the selective formation of trans-pulegenic acid. In the aqueous system only acids are formed, and since these are not labile, the stereochemistry is retained.

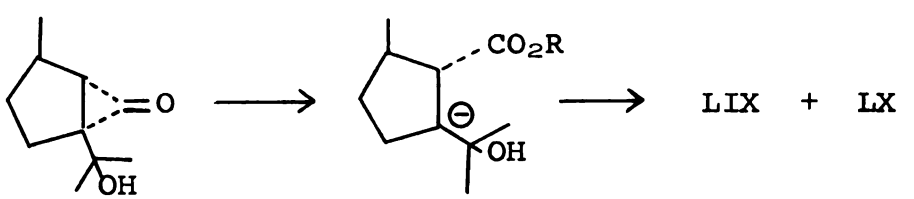
The pulegone oxide used by Cavill (53) was obtained by the action of alkaline hydrogen peroxide on pulegone, and was assumed to be a single stereoisomer, since it melted sharply at ca. 40°, gave one peak on gas chromatography, and showed a single carbonyl stretching absorption in the infrared. After

inspecting models, Cavill assigned configuration LVIII to this material. Treatment of the epoxide with ethanolic sodium ethoxide gave a 20% yield of two acidic products which were shown to be trans, cis-puleganolide (LIX) and trans, trans-puleganolic acid (LX) (eq. 48). These products would be

(48) 

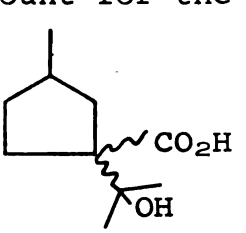
LVIII LIX LX

expected from a stereospecific transformation of isomer LVIII to the cyclopropanone intermediate LXI. Abnormal opening of LXI gives a tertiary anion which may be protonated from either side (eq. 49).

(49) 

LXI

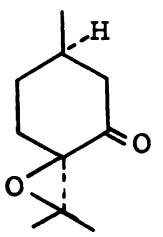
Treatment of LVIII with sodium hydroxide in aqueous ethanol gave LXII, as an epimeric mixture. This may be formed by a normal opening of the cyclopropanone intermediate to give a secondary anion. To account for the observed mixture of



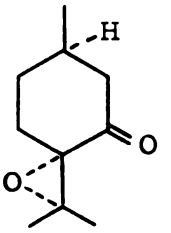
LXII

products, Cavill suggested formation of both possible cyclopropanone intermediates via an initially formed zwitterionic species.

Reusch and Johnson (56) have reported that the pulegone oxide modification having a mp of 40° is actually a mixture of stereoisomers; and they were able to isolate each of the pure isomers (mp 59° and 55°). On the basis of n.m.r. spectra, optical rotatory dispersion curves, thermal isomerization, and a consideration of available conformations, the following assignments were made:



m. 59°



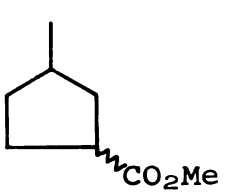
m. 55°

A Favorskii reaction of these isomers, if stereospecific, would provide firm chemical evidence for or against this assignment.

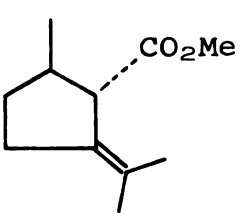
RESULTS AND DISCUSSION

Treatment of pulegone oxide (**LXIII**, m. 57°) with a 4-fold excess of sodium methoxide in boiling glyme gave a 70% yield of acidic products. The glyme used in this experiment was found to contain 0.25-0.30% water, roughly 0.6 molar equivalent of the sodium methoxide used. The remaining neutral product was analyzed by vapor phase chromatography (v.p.c.), and contained no starting material.

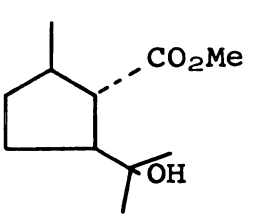
The acids were converted to methyl esters by treatment with excess diazomethane and were separated into three components by v.p.c. These were shown to be an epimeric mixture of methyl 3-methylcyclopentanecarboxylates (**LXV**, 21%), methyl trans-pulegenate (**LXVIA**, 29%), and methyl trans, trans-puleganolate (**LXVIIA**, 50%). The infrared and nuclear magnetic resonance (n.m.r.) spectra were in agreement with the above



LXV



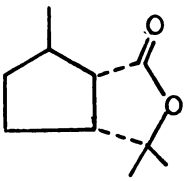
LXVIA



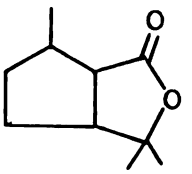
LXVIIA

structures. **LXVIIA**, a new compound, showed absorption at 3500 and 1730 cm^{-1} in the infrared. The n.m.r. spectrum exhibited a doublet at τ 8.98 (J=6c.p.s., area 3), a singlet at τ 8.90 (area 6), a singlet at τ 6.37 (area 3), and broad

absorption from τ 7.5 to 8.8. Upon treatment with methanolic hydrochloric acid, both **LXVIA** and **LXVIIA** were converted to the known cis, trans-puleganolide (**LXVIIIA**). No cis, cis-puleganolide (**LXVIIIB**) was observed.

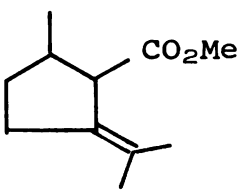


LXVIIIA

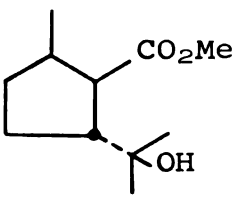


LXVIIIB

Reaction of the lower melting pulegone oxide isomer (**LXIV**, m.54°) under identical conditions gave a mixture of acids in 83% yield. After esterification with excess diazomethane, this mixture was separated by v.p.c. analysis into five components: the epimeric methyl 3-methylcyclopentanecarboxylates (**LXV**, 15%), a mixture of methyl cis- and trans-pulegenates (**LXVIA** and B, 23%), methyl trans, cis-puleganolate (**LXVIIB**, 33%), cis,trans-puleganolide (**LXVIIIA**, 22%), and an unidentified component (8%).



LXVIB



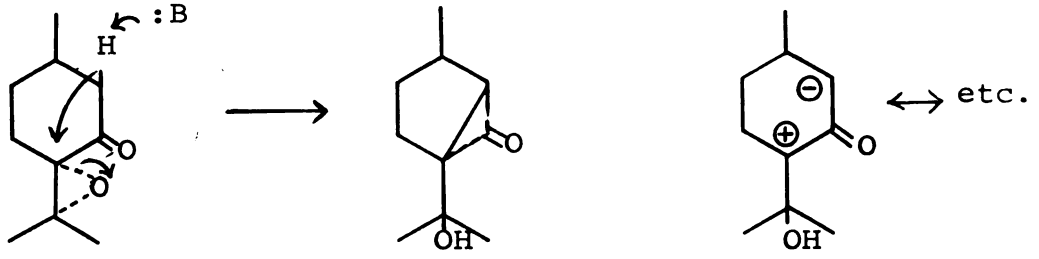
LXVIIB

These structure assignments are supported by infrared and n.m.r. spectra. **LXVIIB** showed absorption at 3500 and 1730 cm^{-1} in the infrared. The n.m.r. spectrum exhibited a doublet

at τ 9.12 (J=6.5c.p.s., area 3), a singlet at τ 8.98 (area 6), a singlet at τ 6.37 (area 3), and broad absorption from τ 7.1 to 8.4. The methyl pulegenate mixture was converted by methanolic hydrochloric acid into a mixture of the stereoisomeric puleganolides (**LXVIIIA** and B). In a similar manner, **LXVIIB** was converted to cis,cis-puleganolide (**LXVIIIB**); no cis, trans-puleganolide was formed. Methyl cis-pulegenate (**LXVIB**) was also formed in this reaction.

These results are best explained by a stereospecific formation and cleavage of a cyclopropanone intermediate. According to this mechanism, the epoxide is directly displaced by an α'-anion leading, in the case of isomer **LXIII**, to intermediate **LXXA** (eq. 50). A zwitterionic intermediate (**LXXI**)

(50)

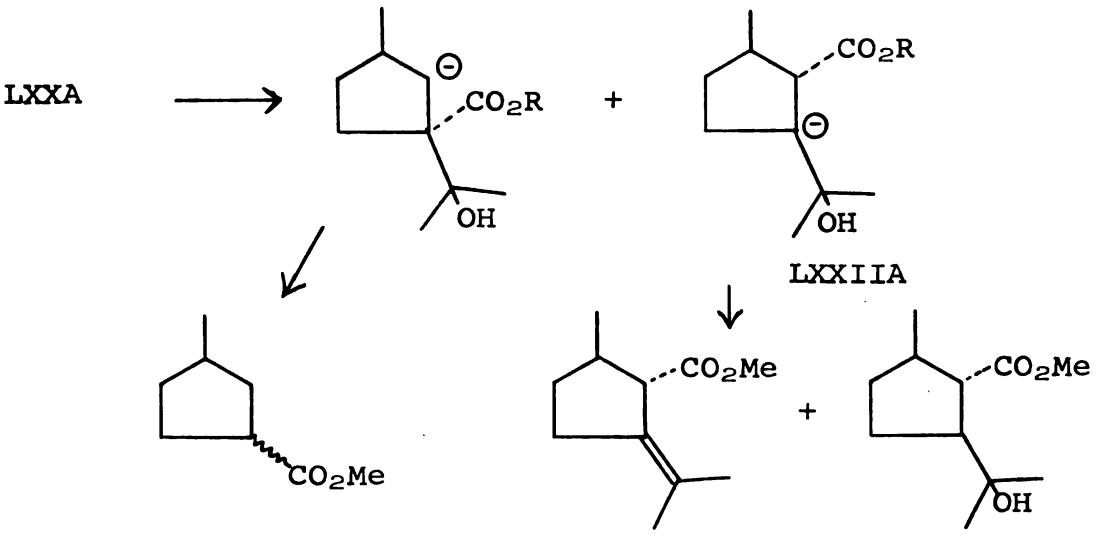


LXIII **LXXA** **LXXI**

would be common to both isomeric pulegone oxides, and the same mixture of products would be expected from each isomer.

The cyclopropanone intermediate may be opened by base in two ways, one to give a secondary anion, the other to give a tertiary anion beta to the hydroxyl group (**LXXIIA**) (eq. 51). The former mode of opening is apparent in ca. 20% of the

(51)



LXV LXVIA LXVIIA

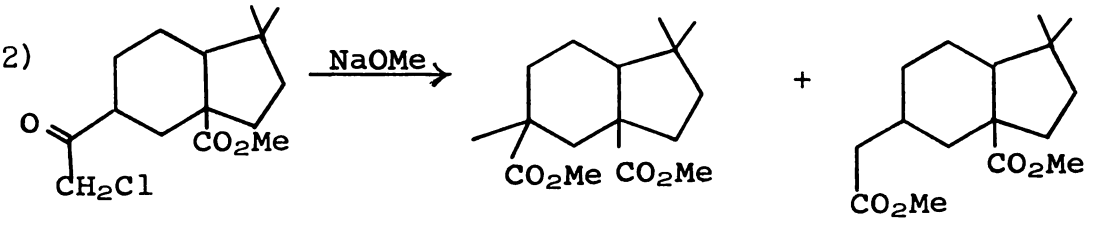
products. Protonation of the secondary anion, followed by retroaldolization, would lead to **LXV**; that this material is an epimeric mixture is not surprising, since the reverse aldol reaction would not be stereospecific. The latter mode of opening (eq. 51) predominates by roughly 4 to 1. Loss of hydroxide ion from **LXXIIA** would lead to **LXVIA**; a stereospecific protonation with retention of configuration would give **LXVIIA**. Competition between these two reactions is reasonable, due to the small concentration of proton donating species in the solvent. Cavill and Hall (57) have now extended their study of the reaction of the pulegone oxides in ethanolic sodium ethoxide, and report that no pulegenic acids are found. In this proton donating solvent the anionic intermediates would be immediately protonated, and elimination of hydroxide ion becomes unlikely. That **LXVIA** was not formed during the acidic portion of our work-up was proven by treating pure **LXVIIA** under

the same conditions. Only unchanged starting material was recovered.

The predominant direction of opening of the cyclopropanone intermediate is opposite to that found in Favorskii reactions of α-halo ketones (29). These compounds yield products arising from the formation of the less substituted anion. (Discrete carbanions may not be formed in these reactions; however, some carbanion character must reside on the α-carbon atom.) In epoxy ketones, however, the anion beta to the hydroxyl group seems to be preferentially formed. In the case of piperitone oxide (L)(45,47,49) and carvenone oxide (LI) (46), this anion is the less substituted of the two possibilities; however, the Favorskii reaction of 5β,6β-epoxycholestan-4-one (LV) proceeds via a tertiary anion at C_5 (51). This mode of reaction may be due to inductive stabilization of the β-anion by the hydroxyl group. Alternatively, the polar hydroxyl group may orient solvent molecules closer to the α-carbon, resulting in stabilization of the forming anion by solvation.

An interesting abnormal Favorskii product was observed by Kundu et al. (58). α-Chloroketone LXXIII gave only a poor yield of the expected product (LXXIV), while LXXV was found to be the major product (eq. 52). If this reaction proceeds

(52)



LXXIII LXXIV LXXV

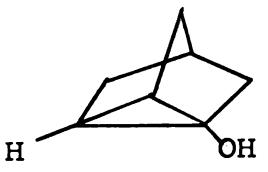
via a cyclopropanone mechanism, the ring-opening step must occur predominantly to give the more substituted anion; however, the carbomethoxy group would not be expected to exert a significant inductive effect over three carbon atoms. Alternatively, **LXXV** may be formed by a competing semi-benzylic mechanism.

The stereospecificity of the protonation of **LXXIIA** is surprising. Random protonation would result in a mixture of **LXVIIA** and **LXVIIIA**. Since a mixture of puleganolides **LXVIIIA** and B was found to be unchanged when submitted to the Favorskii reaction conditions, the protonation is indeed stereospecific, and **LXVIIIA** is never formed. The observed retention of configuration during ring opening is in accord with the principles of carbanion substitution as formulated by Cram (59). According to this study, the stereochemistry of products resulting from heterolytic carbon-carbon bond cleavage depends on the solvent and the cation accompanying the base. In solvents of low dielectric constants and with alkali metal cations a high degree of retention of configuration was observed. The use of solvents of high dielectric constants, as well as quaternary ammonium bases in solvents of low dielectric constants, gave complete racemization. Protic solvents of high dielectric constants gave moderate inversion of configuration.

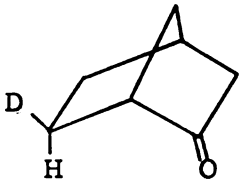
An opposite stereochemical result has been reported by Nickon et al. (60). Treatment of 1-hydroxynortricyclene (**LXXVI**) with potassium tert-butoxide in tert-butyl alcohol-O-d_1

gave > 94.5% 6-exo-d-norbornan-2-one (LXXVII), corresponding to inversion of configuration at C_6 (eq. 53). Similar results

(53)



LXXVI

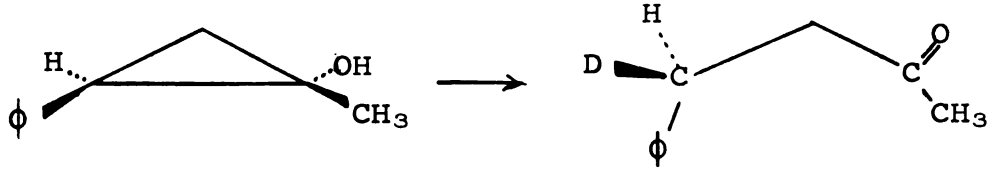


LXXVII

were obtained when LXXVI was treated with potassium methoxide in methanol-O-d_1 and in a DMSO-methanol-O-d_1 mixture, or with tetramethylammonium deuteroxide in deuterium oxide.

DePuy and co-workers (61) have examined the reaction of 1-methyl-trans-2-phenylcyclopropanol (LXXVIII) with sodium deuteroxide in a 50:50 mixture of deuterium oxide and dioxane, and report complete inversion of configuration in the product (eq. 54). These results are in qualitative agreement with the

(54)



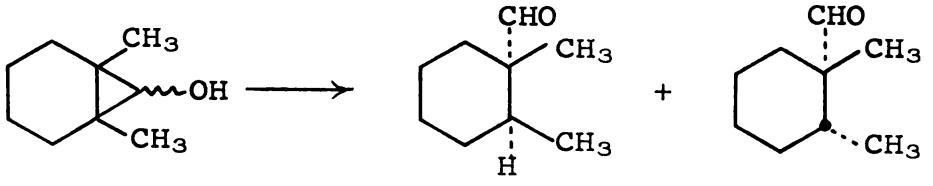
LXXVIII

studies of Cram (59), in which the use of a protic solvent of high dielectric constant is predicted to result in substantial inversion.

The base-catalyzed opening of endo- (LXXIXa) and exo-7-hydroxy-1,6-dimethyl[4.1.0]bicycloheptane (LXXIXb) has been examined by Wharton and Bair (62). Treatment of either LXXIXa or b with potassium tert-butoxide in tert-butyl alcohol gave

1,2-dimethylcyclohexanecarboxaldehyde (**LXXX**) having > 90% retention of configuration at the C_2-carbon. With ethylene glycol and its sodium salt, **LXXIX**a gave a cis-trans mixture of **LXXX** corresponding to 40% inversion, while **LXXIX**b gave 70% inversion (eq. 55). Again, these results are consistent

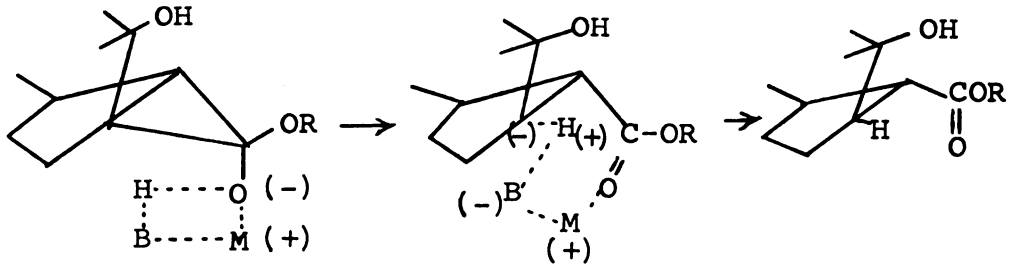
(55)



LXXIX **LXXX**

with the observations of Cram, with the exception of the dependence of the product ratio on the configuration of the leaving group. Cram et al.(63) found identical stereochemical results from the basic cleavage of two pairs of diastereomers, 1,2-diphenyl-2-methyl-1-butanol and 2,3-diphenyl-3-methoxy-2-butanol. Wharton and Bair (62) suggested that the difference in product ratios is due to the formation of conformationally different cyclohexane chairs from the isomeric starting materials.

Thus, it may be concluded that there is no evidence for a novel mechanism due to the unusual properties of the cyclopropane ring. The mechanism presented in eq. 56 for **LXIII** is based on Cram's suggestions. The neighboring hydroxyl group is a factor which was not present in any of Cram's examples.

(56) 

It is improbable that this group exerts a significant influence on the direction of protonation, since it can orient solvent molecules toward either side of the incipient carbanion. In this regard, predominant retention of configuration is also observed when the reaction is effected in ethanol (57).

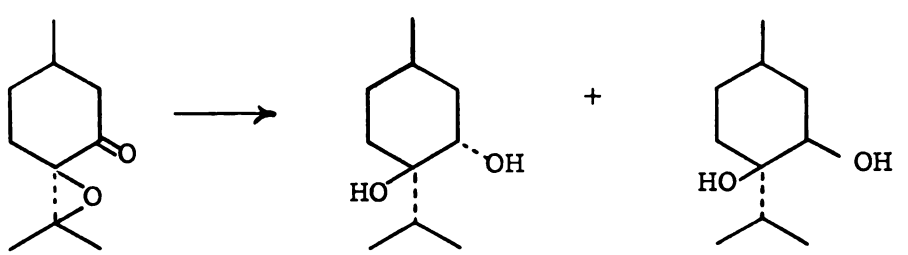
While the products obtained from **LXIII** are exclusively those which would be predicted from a stereospecific Favorskii reaction, the products obtained from **LXIV** are not. Cavill (57) has shown that treatment of **LXVIIB** with ethanolic sodium ethoxide results in incomplete conversion to cis, trans-puleganolide (**LXVIIIA**). Thus, the hydroxy acid initially formed in the reaction is epimerized to the observed "non-stereospecific" product. It is believed that trans-pulegenic acid arises from the cis-isomer by a similar pathway.

The absence of cis-pulegenic acid from the rearrangement of **LXIII** is somewhat surprising, since Wolinsky (64) has shown that methyl trans-pulegenate (**LXVIA**) is epimerized by methanolic sodium methoxide to give a 23:77 ratio of cis and trans methyl pulegenates, respectively. Either opening of the cyclopropanone is effected by hydroxide ion, leading to

an acid which is resistant to epimerization or the ester is hydrolyzed much faster than it is epimerized.

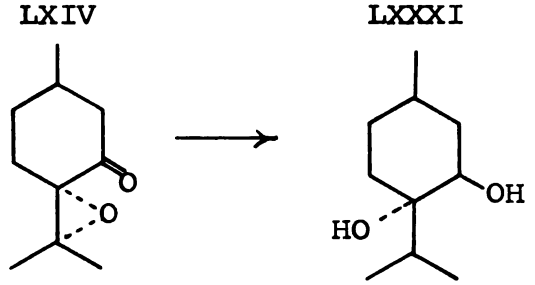
The stereospecific Favorskii reaction of the pulegone oxide isomers permits the unambiguous assignment of their configurations. In isomer **LXIII**, m. 57°, the C_1-methyl and the epoxide oxygen bear a trans-relationship, and in isomer **LXIV**, m. 54°, they bear a cis-relationship. This assignment is the reverse of that previously made (56). These assignments have recently been confirmed by Katsuhara (65). Lithium aluminum hydride reduction of **LXIV** gave a mixture of (+)-trans-4-hydroxyneomenthol (**LXXXI**) and (+)-cis-4-hydroxymenthol (**LXXXII**), both known compounds (eq. 57). Reduction of **LXIII** gave only (-)-trans-4-hydroxyneoisomenthol (**LXXXIII**) (eq. 58).

(57)



LXIV **LXXXI** **LXXXII**

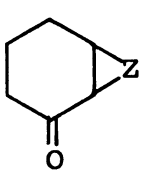
(58)



LXIII **LXXXIII**

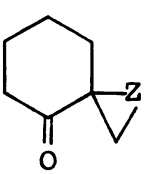
While the configurations of the pulegone oxide isomers have now been established, the problem of a conformational analysis consistent with the spectral data remains.

The interpretation of the optical rotatory dispersion (O.R.D.) and circular dichroism (C.D.) spectra of α,β-epoxy ketones is complicated by two factors. First it must be determined whether the conjugated epoxy ketone system is an inherently dissymmetric chromophore (as is the case with certain enones). Such chromophores are usually characterized by relatively large rotational strengths. Second, the sign of the rotatory contribution of a chiral epoxy ketone system must be resolved. In this regard, Djerassi and co-workers (66) have presented extensive evidence for a reversal of the Octant Rule in its application to epoxy ketones and cyclopropyl ketones having fused rings of type LXXXIV. Here, it appears that the epoxy ketone acts as a single, integrated



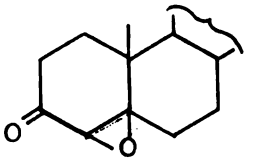
LXXXIV

Z = O, CH_2.

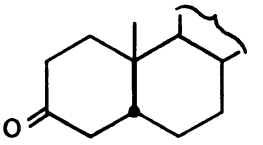


LXXXV

chromophore having inherent dissymmetry, this condition being reflected in increased amplitudes and a reversal of the Cotton effect sign. An example of this phenomenon is found in the comparison of 4β,5β-epoxycholestan-3-one (LXXXVI) with 5β-cholestan-3-one (LXXXVII). LXXXVII exhibits a molecular ellipticity of [θ] = -1,500 (67), while LXXXVI has [θ] = +12,400 (R_o=12.5 x 10^{-40}c.g.s.). In this case, introduction



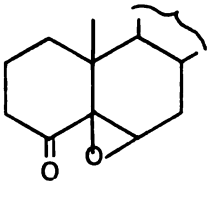
LXXXVI



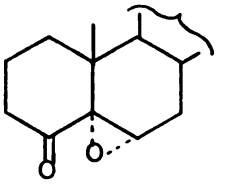
LXXXVII

of a fused epoxide ring has resulted in a change in sign of the Cotton effect with an attendant increase in magnitude. Extension of this reversal to compounds having the 3-membered ring spiro to the carbonyl-carrying ring (type LXXXV) was based on only a few examples, and must be regarded as tenuous. In systems of this type, substituents on the epoxide ring may occupy a near octant, thus reversing the sign of their contribution to the rotational strength of the chromophore.

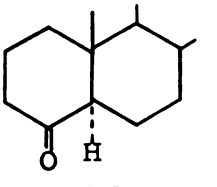
Since the pulegone oxides are of the spiran type, the sign of the Cotton effect for a given conformation is difficult to predict. In order to provide rigid models for this system, 5α,6α-epoxycholestan-4-one (LXXXVIII) and 5β,6β-epoxycholestan-4-one (LXXXIX) were synthesized, and their O.R.D. and C.D.



LXXXIX



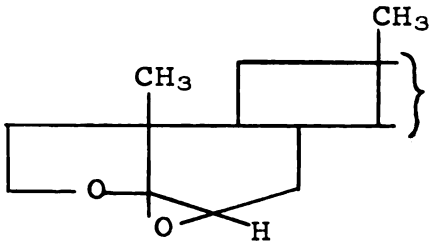
LXXXVIII



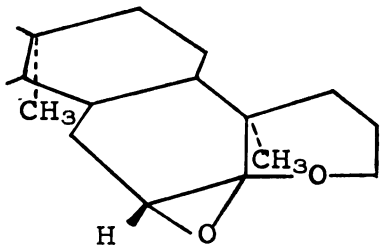
XC

spectra were taken. Examination of Drieding models indicates that in LXXXVIII, the epoxy ketone is locked in conformation LXXXVIIIa. Application of the Octant Rule in a normal fashion predicts a moderate negative Cotton effect for this conformation,

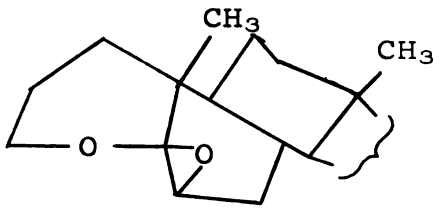
since the steroid residue occupies a negative octant, while the epoxide oxygen lies in a positive octant. The only substituent which lies in or near a front octant is the C_8-hydrogen; and no significant contribution to the rotational strength is expected. An inspection of models discloses that **LXXXIX**



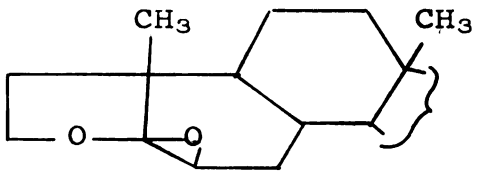
LXXXVIIIa



LXXXIXa



LXXXIXb



LXXXIXc

is more flexible than **LXXXVIII**. Three conformations involving changes in ring A configuration are easily discerned. One is a chair (**LXXXIXc**) and two are twist boat forms (**LXXXIXa** and b). On the basis of non-bonded interaction measurements with Dreiding models, **LXXXIXa** is predicted to be the most stable conformation. In this case, the Octant Rule would predict a moderate positive Cotton effect, the steroid residue lying in a positive octant, and the epoxide oxygen occupying

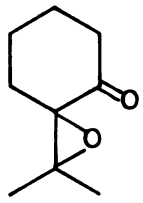
a negative octant. The other conformations would, by a similar analysis, have a predicted negative Cotton effect. Calculated (68a) rotational strengths were in accord with the above predictions: **LXXXIX**, R_o= 2.02 x 10^{-40}c.g.s. (95% EtOH), R_o= 2.31 x 10^{-40}c.g.s. (cyclohexane); **LXXXVIII**, R_o= -2.38 x 10^{-40} c.g.s. (95% EtOH), R_o= -2.53 x 10^{-40}c.g.s. (cyclohexane). Application of the reversed Octant Rule would predict an intense Cotton effect of reversed sign for each of these compounds. For comparison the rotational strength of 5α-cholestan-4-one (**XC**) (R_o= -4.15 x 10^{-40}c.g.s.) (69) is of the same sign as, and larger than that of the corresponding epoxide (**LXXXVIII**). Thus, the abnormal behaviour of fused epoxy ketones is not observed in these spiran-type compounds.

It is known that the chemical shifts of the protons in a ketone vary upon changing the solvent from CCl_4 to benzene. Recently, an empirical rule has been formulated which correlates the direction of this variation with the location of the substituent relative to the carbonyl group (70-72). The chemical shift difference (Δ) is defined in eq. 59.

(59) $$\Delta = (\tau_{\phi H} - \tau_{CCl_4}) \text{ p.p.m.}$$

Those substituents located behind a plane perpendicular to the carbonyl bond and passing through the carbonyl carbon will exhibit a positive Δ; those located in front of the plane will exhibit a negative Δ. The chemical shifts of the geminal methyls of the pulegone oxide isomers and those of nor-pulegone

oxide (XCI) in benzene and CCl_4 are summarized in Table 1.



XCI

It may be concluded from this data that in all cases the methyls lie on or behind the reference plane. Since this plane in turn lies behind the plane separating near and far octants in the Octant Rule (68b), the Cotton effect of the pulegone oxides must be explained solely in terms of contributions from the far octants.

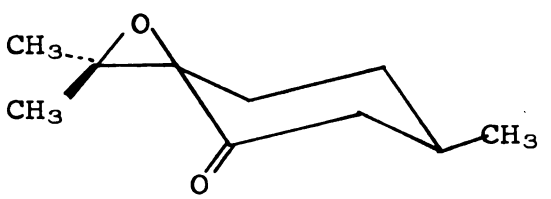
Table 1. Geminal Methyl Chemical Shifts[a]

Compound	Benzene(τ)	CCl_4(τ)	(p.p.m.)
LXIII	8.90	8.88	+0.02
	8.78	8.63	+0.15
LXIV	8.88	8.84	+0.04
	8.79	8.64	+0.15
XCI	8.96	8.88	+0.08
	8.87	8.64	+0.23

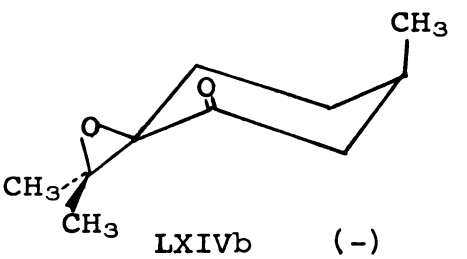
[a]See reference 73.

An examination of Dreiding models indicates that chair conformations of the pulegone oxides are probably favored over boat and twist-boat conformations. In the case of the lower melting isomer these are LXIVa and LXIVb, and in the higher

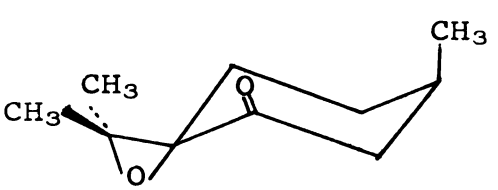
melting isomer they are **LXIIIa** and **LXIIIb**. Application of the Octant Rule in a normal manner would predict **LXIVa** and **LXIIIb** to be positive, and **LXIIIa** and **LXIVb** to be negative. The O.R.D. and C.D. spectra of **LXIII** exhibit a positive Cotton



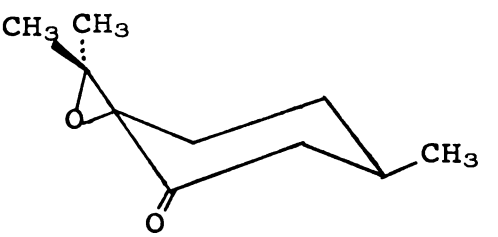
LXIVa (+)



LXIVb (-)



LXIIIa (-)



LXIIIb (+)

effect of rotational strength 2.64 x 10^{-40}c.g.s. (95% EtOH), 1.97 x 10^{-40}c.g.s. (cyclohexane). In addition, **LXIII** exhibits a temperature dependence in EPA (5:5:2 ether:isopentane: alcohol) (74): $[\theta]_{305}^{25^{\circ}} = 3257$, $[\theta]_{304}^{-74^{\circ}} = 2442$, $[\theta]_{303}^{-192^{\circ}} = 2153$. Two explanations are consistent with these results. Either an equilibrium is occurring between **LXIIIb** and some solvated species which has a smaller positive rotational strength (a decrease in temperature favors the more weakly rotating solvated species, resulting in a net decrease of rotational

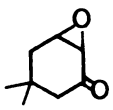
strength), or **LXIIIb** may be in equilibrium with another conformation which has a greater, positive rotational strength but which is less stable. A lowering of the temperature in the latter case would favor **LXIIIb** and result in a decrease of the rotational strength. While a choice between these two explanations is not possible, it appears that **LXIIIb** is the predominant conformer at room temperature.

The **C.D.** spectrum of **LXIV** in 95% ethanol exhibits a negative Cotton effect at 305 mμ (R_o = -0.597 x 10^{-40}c.g.s.) and a weakly positive Cotton effect at 270 mμ (R_o= 0.141 x 10^{-40} c.g.s.). In cyclohexane the **C.D.** shows some fine structure, the rotational strengths being -0.422 x 10^{-40}c.g.s. and +0.036 x 10^{-40}c.g.s., respectively. A temperature dependence is also observed in EPA (74): $[\theta]_{308}^{25^o}$ = -963, $[\theta]_{275-7}^{25^o}$= +252, $[\theta]_{308-10}^{-74^o}$= -1104, $[\theta]_{278}^{-74^o}$ = +359, $[\theta]_{312}^{-192^o}$ = -453, $[\theta]_{285}^{-192^o}$ = +1411. Djerassi and co-workers have shown that "a C.D. curve with two oppositely signed extrema separated by ca. 30 mμ will arise whenever two Cotton effects of similar amplitudes, but opposite sign, are superimposed with their individual maxima separated by 1 to 20 mμ" (75). Furthermore, the rotational strengths of the resulting Cotton effects are diminished in comparison to their individual rotational strengths. It is also known that a solvated ketone will usually exhibit an $n \rightarrow \pi^*$ absorption at shorter wavelengths than the corresponding unsolvated species. Thus, in **LXIV** the positive band at the shorter wavelength is probably due to a solvated species, since it increases upon

lowering the temperature. It should also be noted that this band decreases markedly on going from 95% ethanol to cyclohexane. The negative extremum shows an abnormal temperature dependence, the rotational strength increasing from 25° to -74° and decreasing from -74° to -192°. The simplest explanation of this phenomenon involves an equilibrium between **LXIVb** and some other less negative conformation at 25°. Lowering the temperature to -74° favors the more stable conformation (**LXIVb**), resulting in a net increase in rotational strength. A further decrease in temperature to -192° results in extensive conversion of **LXIVb** to the solvated species. Thus, at room temperature, the predominant conformation is probably **LXIVb**.

The ultraviolet absorption maxima and carbonyl stretching frequencies of a number of epoxy ketones are listed in Table 2.

Table 2. Infrared and Ultraviolet Spectra

Compound	$\nu_{C=O}^{CCl_4}$ (cm^{-1})	$\lambda_{max}^{Cyclohexane}$ mμ(ε)
LXXXVIII	1711	304 (44.5)
LXXXIX	1725	297 (37.7)
LXXXVI	1710	304 (32.1)
		313 (31.7)
LXIII	1725	302 (33.8)
LXIV	1726	303.5 (31.4)
Isophorone Oxide[a]	1717	303 (24.5)
 a	1720	302.5 (19.9)
 a	1747	303.5 (26.0)
 a	1750	305 (23.0)

[a]Sample furnished by Mr. Charles Markos, Mich. State Univ.

Little can be concluded from the ultraviolet maxima, since the relative configuration of the ketone and epoxide functions has no apparent effect on either the wavelength or the extinction coefficient. Similarly, no correlation can be made for the carbonyl stretching frequencies, since some similar configurations have different frequencies, and different configurations have similar frequencies.

The pulegone oxides exhibit significant differences in the n.m.r. spectrum, especially the low field portion (see Figure 1). Isomer **LXIV** displays a broad two proton doublet at τ 7.68, while **LXIII** shows a single proton multiplet centered at τ 7.51 that appears to be the low field portion of an **ABC** spectrum. The previous assignment of these low field resonance signals to the C-2 hydrogen atoms (56) has now been confirmed by deuterium exchange in mild alkaline solution.

Eliel and co-workers (76) have examined the effect of methyl substituents on the chemical shift of the α-hydrogen in various cyclohexanols. The introduction of an axial methyl at C-2 deshielded an axial α-hydrogen by 11.5 c.p.s., while an equatorial α-hydrogen was shielded by 24 c.p.s. An equatorial methyl at C-2 shielded an axial α-hydrogen by 28 c.p.s., while an equatorial α-hydrogen was shielded by 17 c.p.s. If these substituent values are applied to the pulegone oxide conformers **LXIVb** and **LXIIIb**, the position of H_e in **LXIII** can be calculated from the observed methylene resonance in **LXIV**. Both hydrogens in **LXIV** appear at 140 c.p.s. (56) (Chemical

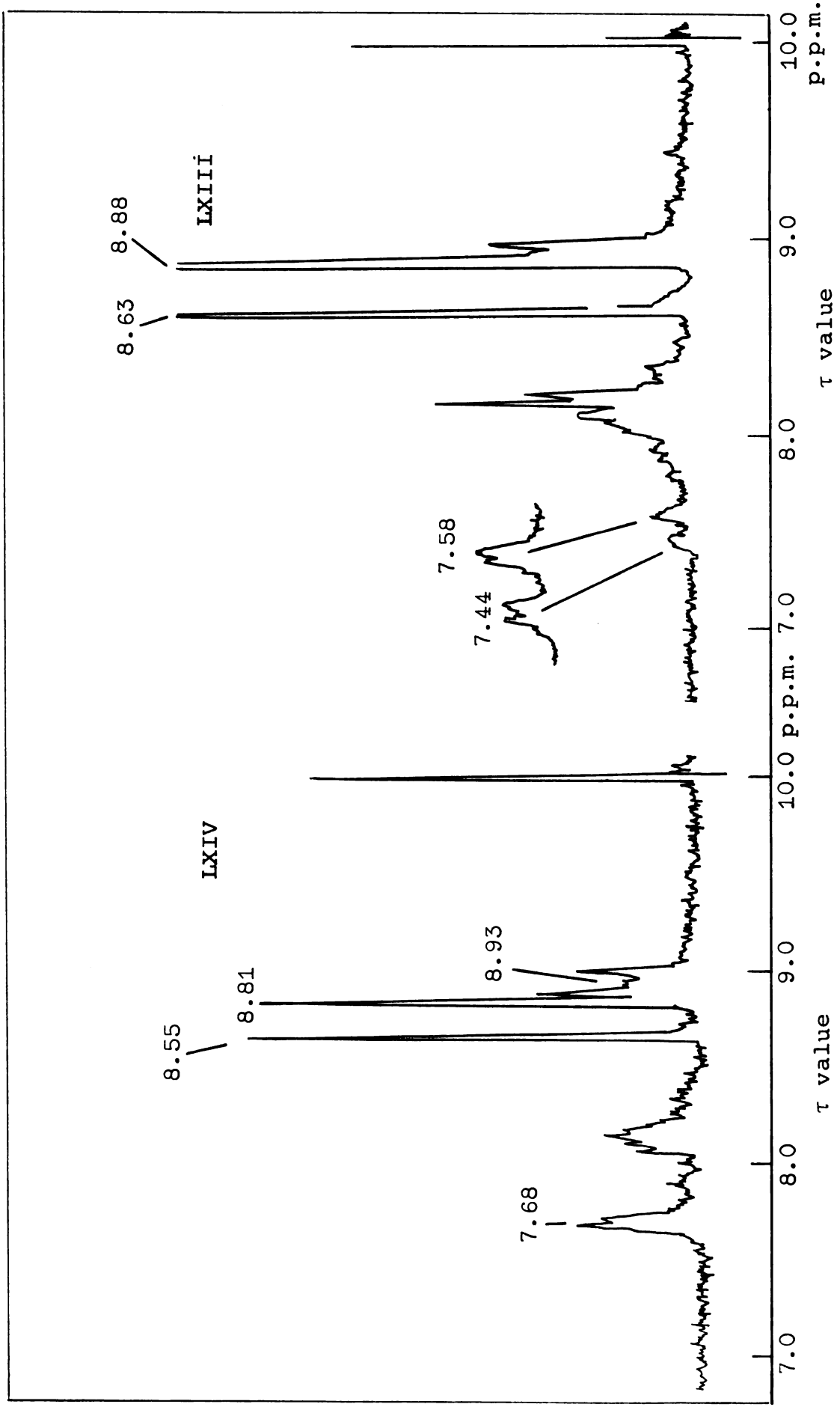


Fig. 1. N.M.R. spectra of the pulegone oxide isomers.

shifts measured from TMS at 60 Mc). Application of Eliel's shielding factors to a change of the methyl from axial to equatorial (LXIV to LXIII) predicts H_e of LXIII to appear at 147 c.p.s. and H_a at ca. 100 c.p.s. In qualitative agreement with these predictions, H_e is observed as a pair of doublets at 145 and 154 c.p.s., and H_a is obscured by the remaining methylene absorptions (< 130 c.p.s.) (56). XCI is conformationally similar to the pulegone oxides, and similar calculations would predict H_e to appear at 167 c.p.s. and H_a at 128 c.p.s. Experimentally, single protons appear at 153 and 145 c.p.s. (73), representing a deviation of 14 and 17 c.p.s., respectively. This discrepancy may be due to the complex splitting of what would be an ABCD system, since the observed values fall between and about the same distance from the predicted values. Thus, while the n.m.r. does not provide firm evidence for conformations LXIIIb and LXIVb, it is not inconsistent with them.

Finally, it should be noted that the thermal isomerization of pulegone oxide favors LXIII over LXIV by a factor of 3:1 (56). This is consistent with the conformational assignments made here, since LXIVb is destabilized by an axial methyl group.

EXPERIMENTAL

Vapor phase chromatographic analyses (v.p.c.) were made with an Aerograph A-90-P instrument. Infrared spectra were determined with a Perkin Elmer 237B spectrophotometer. Nuclear magnetic resonance (n.m.r.) spectra were determined with a Varian associates A-60 high resolution spectrometer, using tetramethylsilane as an internal standard. Ultraviolet spectra were determined with a Carey Model 11 spectrophotometer.

Reagents

Dimethoxyethane (glyme) was obtained from Aldrich Chemical Company. The amount of water present in this solvent was determined by reaction with sodium hydride, the hydrogen evolved being measured by a gas buret. Values from 0.25 to 0.30% were obtained.

Commercial sodium methoxide (Matheson, Coleman and Bell) was used.

Pulegone Oxide

Pulegone oxide isomers LXIII and LXIV were prepared according to the procedure of Reusch and Johnson (56), substituting m-chloroperbenzoic acid for perbenzoic acid. The following spectral properties of LXIII, m. 57°, were obtained:

$\nu_{max}^{CCl_4}$ 1725 cm^{-1}; $\lambda_{max}^{cyclohexane}$ 302 mμ(ε 33.8); O.R.D. in 95% EtOH (c, 0.047), $[\Phi]_{317}$ +2260°, $[\Phi]_{300}$ ±0°, $[\Phi]_{278}$ -2780°; O.R.D. in cyclohexane (c, 0.050), $[\Phi]_{328}$ +1936°, $[\Phi]_{317}$ +925°, $[\Phi]_{310}$ ±0°, $[\Phi]_{290}$ -2080°, $[\Phi]_{285}$ -2103°; C.D. in 95% EtOH (c, 0.047), $[\Phi]_{333}$ ±0, $[\Phi]_{298}$ +3370, $[\Phi]_{254}$ ±0 (R_o=2.64 x 10^{-40} c.g.s.); C.D. in cyclohexane (c, 0.050), $[\Phi]_{345}$ ±0, $[\Phi]_{320}$ +1990, $[\Phi]_{313}$ +2480, $[\Phi]_{309}$ +2560, $[\Phi]_{271}$ ±0 (R_o= 1.97 x 10^{-40}c.g.s.); C.D. in EPA (74) (c, 0.177), $[\Phi]_{305}^{25°}$ +3257, $[\Phi]_{302.5-5}^{-74°}$ +2442, $[\Phi]_{302.5}^{-192}$ +2153 (see Fig. 2). The following spectral properties of LXIV, m. 54°, were obtained: $\nu_{max}^{CCl_4}$ 1726 cm^{-1}; $\lambda_{max}^{cyclohexane}$ 303.5 mμ(ε 31.4); O.R.D. in 95% EtOH (c, 0.049), $[\Phi]_{321}$ -492°, $[\Phi]_{308}$ ±0°, $[\Phi]_{289}$ +1044°; O.R.D. in cyclohexane (c, 0.048), $[\Phi]_{326}$ -297°, $[\Phi]_{320}$ ±0°, $[\Phi]_{303}$ +732°, $[\Phi]_{295}$ +854°, $[\Phi]_{287}$ +753°; C.D. in 95% EtOH (c, 0.049), $[\Phi]_{330}$ ±0, $[\Phi]_{305}$ -984, $[\Phi]_{284}$ ±0, $[\Phi]_{270}$ +247, $[\Phi]_{236}$ ±0 (R_o= -0.597 x 10^{-40} and +0.141 x 10^{-40} c.g.s.); C.D. in cyclohexane (c, 0.048), $[\Phi]_{348}$ ±0, $[\Phi]_{312-7}$ -608, $[\Phi]_{307}$ -643, $[\Phi]_{298}$ -345, $[\Phi]_{287}$ ±0, $[\Phi]_{275-80}$ +78, $[\Phi[_{272}$ +96, $[\Phi]_{266-9}$ +70, $[\Phi]_{256}$ ±0 (R_o= -0.422 x 10^{-40} and +0.036 x 10^{-40}c.g.s.); C.D. in EPA (74) (c, 0.180), $[\Phi]_{308}^{25°}$ -963, $[\Phi]_{275-7}^{25°}$ +252, $[\Phi]_{308-10}^{-74°}$ -1104, $[\Phi]_{278}^{-74°}$ +359, $[\Phi]_{312}^{-192°}$ -453, $[\Phi]_{285}^{-192°}$ +1411 (see Fig. 3).

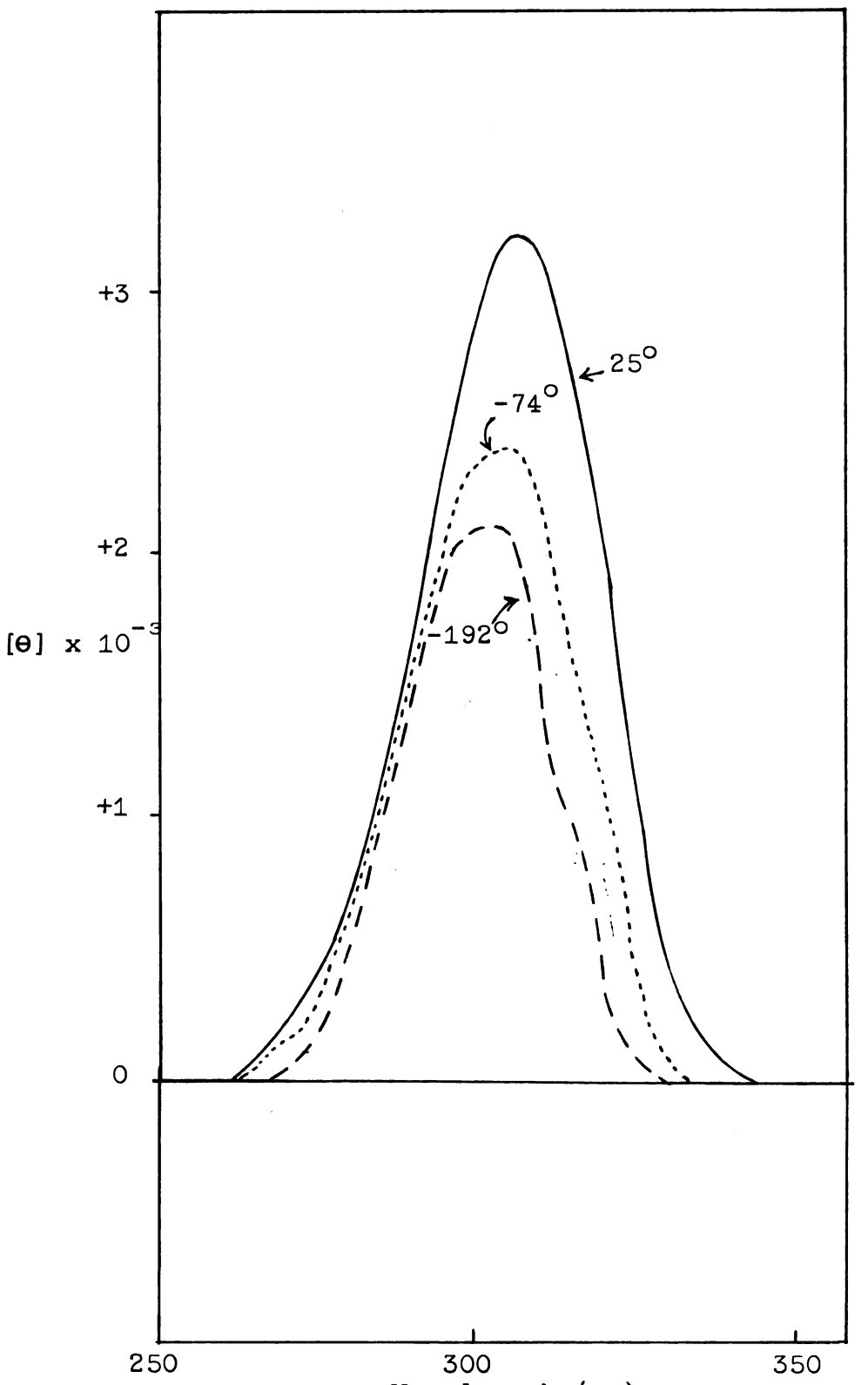


Fig. 2. C.D. spectra of LXIII in EPA.

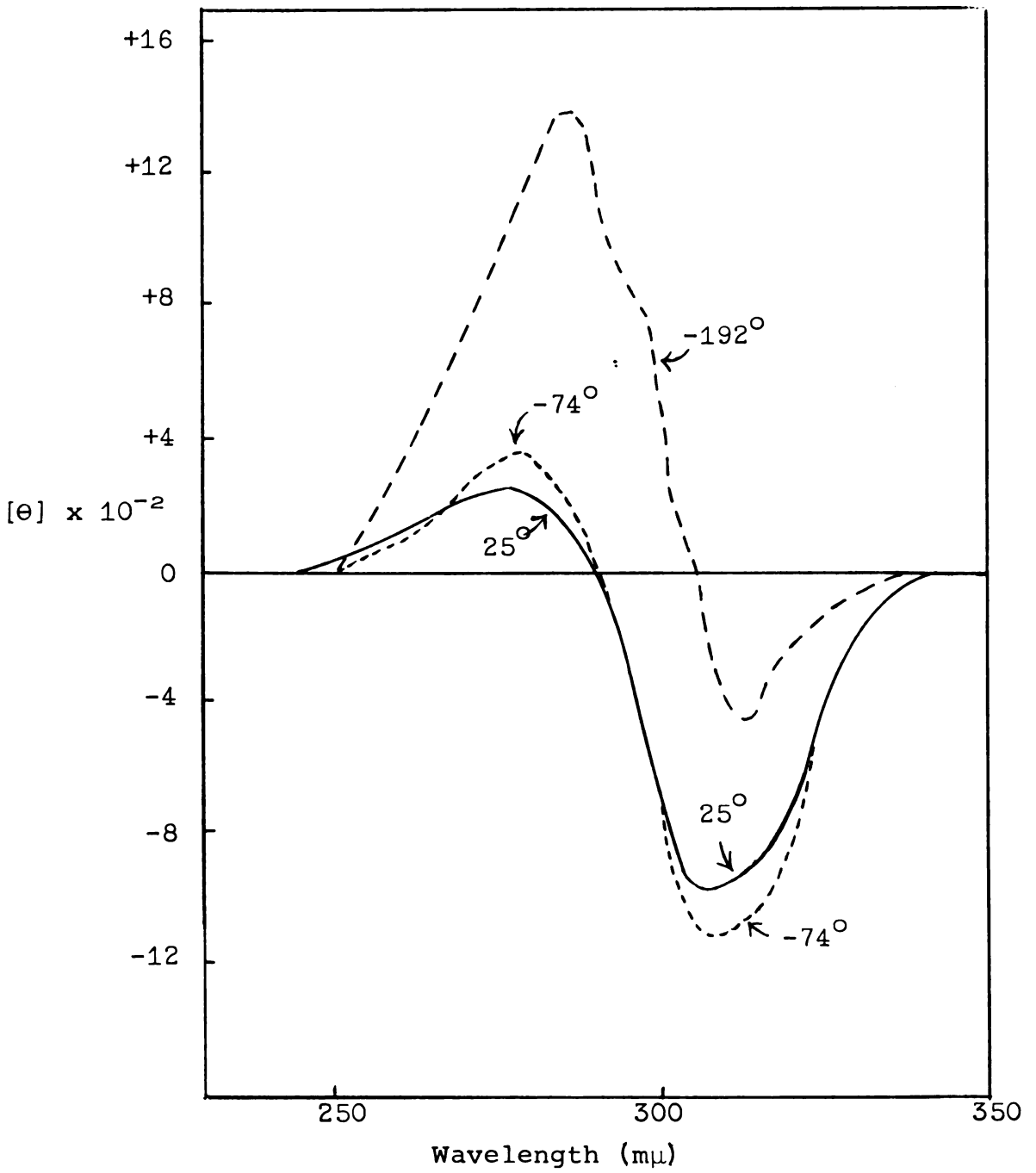


Fig. 3. C.D. spectra of LXIV in EPA.

Favorskii Reaction of Pulegone Oxide LXIII

A. Isolation and Structure Proof of Products

A solution of LXIII (300 mg., 1.8 mmoles) and sodium methoxide (435 mg., 8.0 mmoles) in glyme (30 ml.) was refluxed for 19 hours. After cooling, the mixture was taken up in ether and extracted three times with 10% sodium hydroxide. The combined aqueous portions were acidified with hydrochloric acid (pH < 1), and then extracted with ether. The combined ether extracts, after being washed, dried and evaporated, yielded 210 mg of an oily acidic material.

The original organic layer was washed, dried and evaporated, yielding 115 mg of a light oil. Analysis of this material by v.p.c. (4% QF-1 on 60/80 Chromosorb G at 140°) disclosed that the major component was glyme (ca. 80%); the remaining neutral products (retention times 3.3 and 4.4 min.) exhibited hydroxyl absorption but no carbonyl absorption in the infrared.

The crude acid products were methylated with diazomethane, and analysis (v.p.c. - same conditions) showed three components having retention times of 1.3, 2.5 and 6.5 min. These were identified as LXV, LXVIA and LXVIIA (integrated areas 3:4:7 respectively), by a combination of spectroscopic and chemical evidence.

1. Methyl 3-methylcyclopentane carboxylate. The infrared spectrum of LXV showed carbonyl absorption at 1730 cm^{-1}, but no hydroxyl bands. Only end absorption was observed in the

ultraviolet. The n.m.r. spectrum exhibited a pair of doublets at τ 9.03 and 8.97. ($J \approx 7$ cps, area 3), a singlet at τ 6.41 (area 3) and broad absorption from τ 7.0 to 8.9 (area 8.5).

2. Methyl trans-pulegenate. The infrared spectrum of LXVIA was identical with that of an authentic sample of methyl trans-pulegenate (77). The n.m.r. spectrum exhibited a doublet at τ 8.99 (J=7 c.p.s., area 3), a pair of methyl singlets centered at τ 8.40 and separated by 5 c.p.s. (area 6), a singlet at τ 6.42 (area 3) and broad absorption from τ 7.0 to 8.3 (area 6).

3. Methyl trans,trans-puleganolate. The infrared spectrum of LXVIIA showed hydroxyl absorption at 3500 cm^{-1} and carbonyl absorption at 1730 cm^{-1} (see Fig. 4). The n.m.r. spectrum exhibited a doublet at τ 8.98 (J= 6 c.p.s., area 3), a singlet at τ 8.90 (area 6), a singlet at τ 6.37 (area 3) and broad absorption from τ 7.5 to 8.8 (see Fig. 5).

4. Conversion of methyl trans-pulegenate to cis,trans-puleganolide. A solution of LXVIA (60 mg.) in 2 ml. methanol containing 0.5 ml. conc. hydrochloric acid was refluxed for 7 hours. The reaction mixture was dissolved in ether, washed, dried and concentrated. The oily residue (40 mg.) was analyzed by v.p.c. (5% FFAP on 60/80 Chromosorb G at 150°); the most readily eluted component was unreacted LXVIA (19%), a minor unidentified material (7%) followed and the major product (74%), which was the last to appear, was

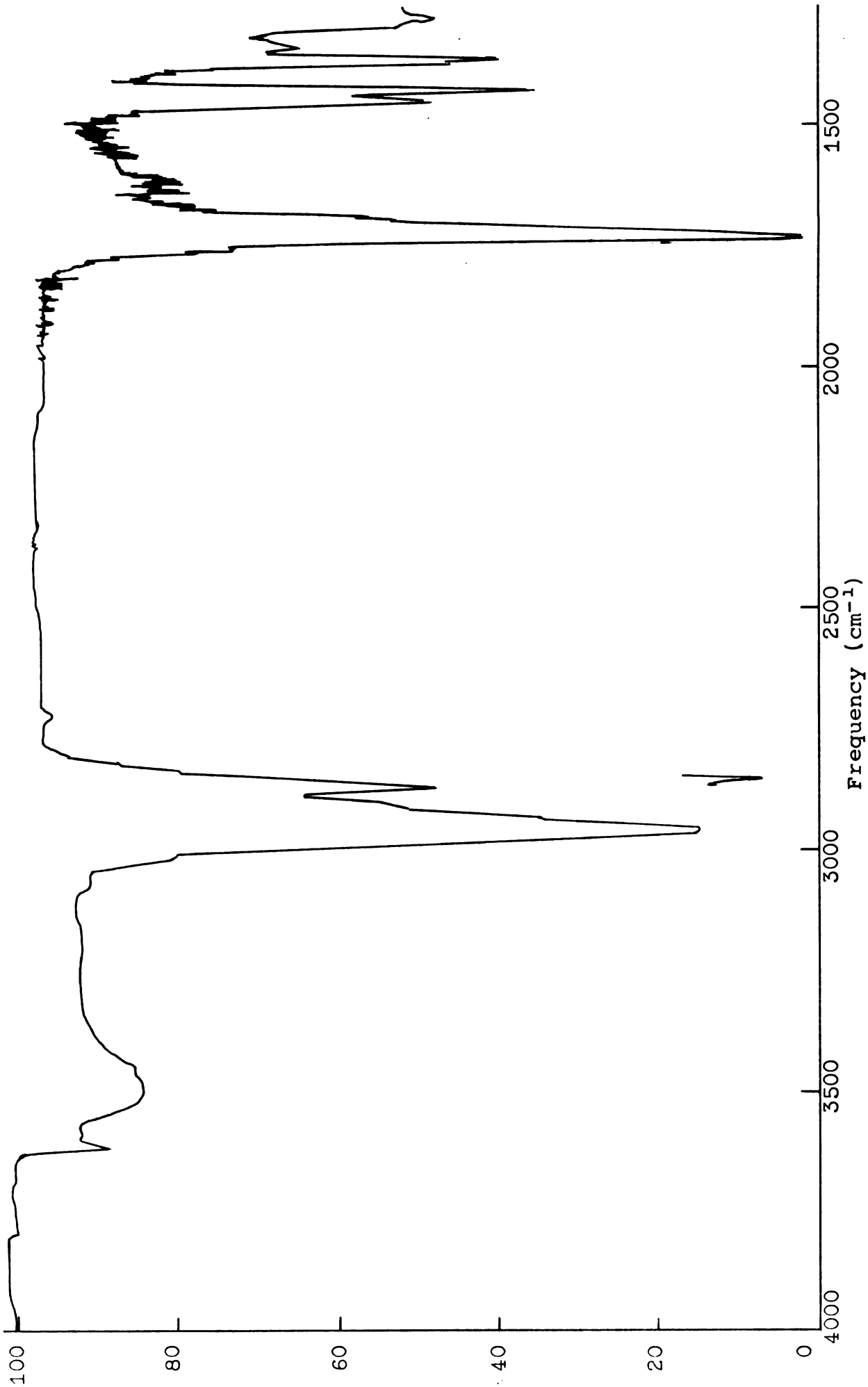


Fig. 4a. Infrared spectrum of methyl trans,trans-puleganolate (LXVIIA) in CCl_4.

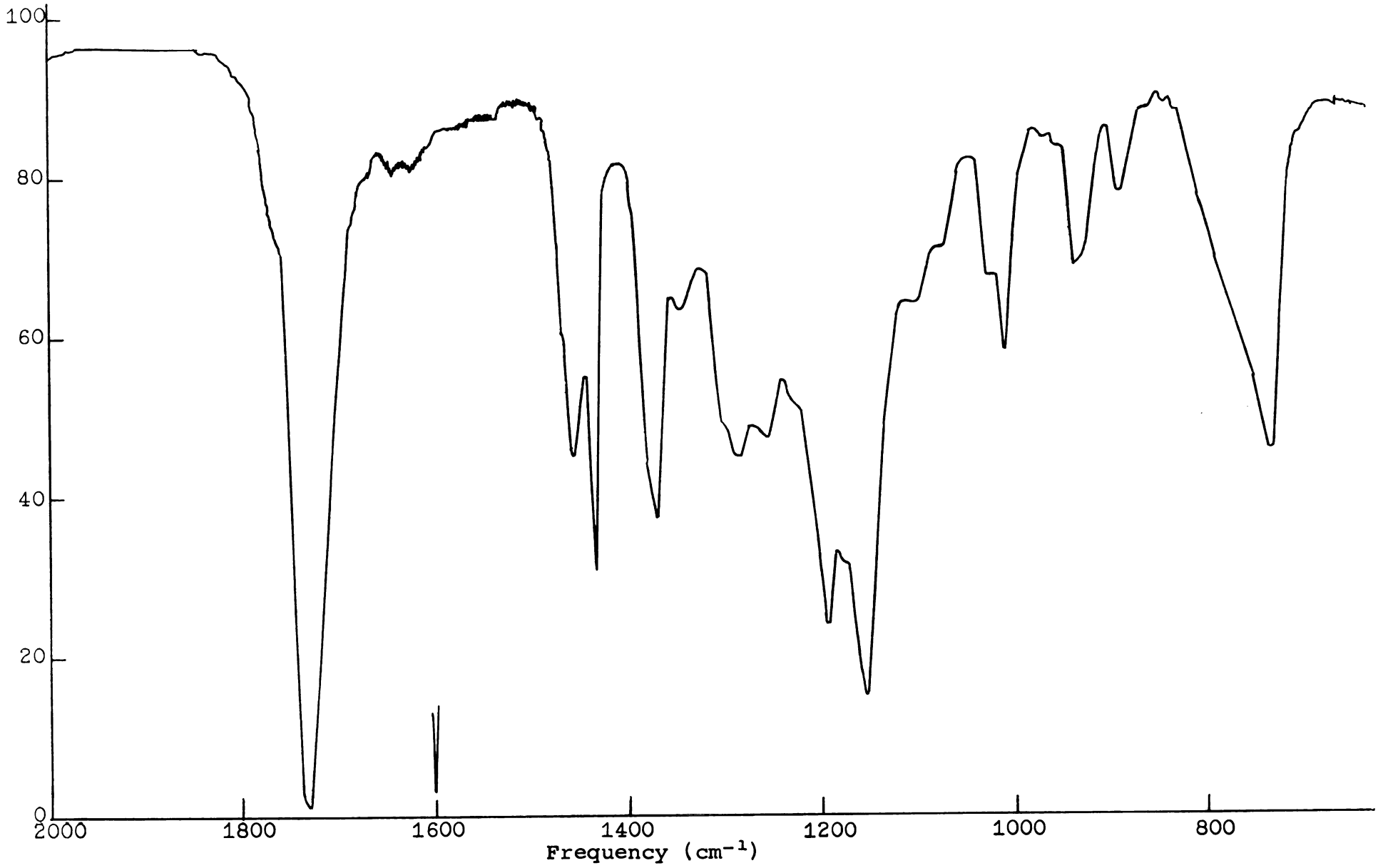


Fig. 4b. Infrared spectrum of methyl trans,trans-puleganolate (LXVIIA) in CCl_4.

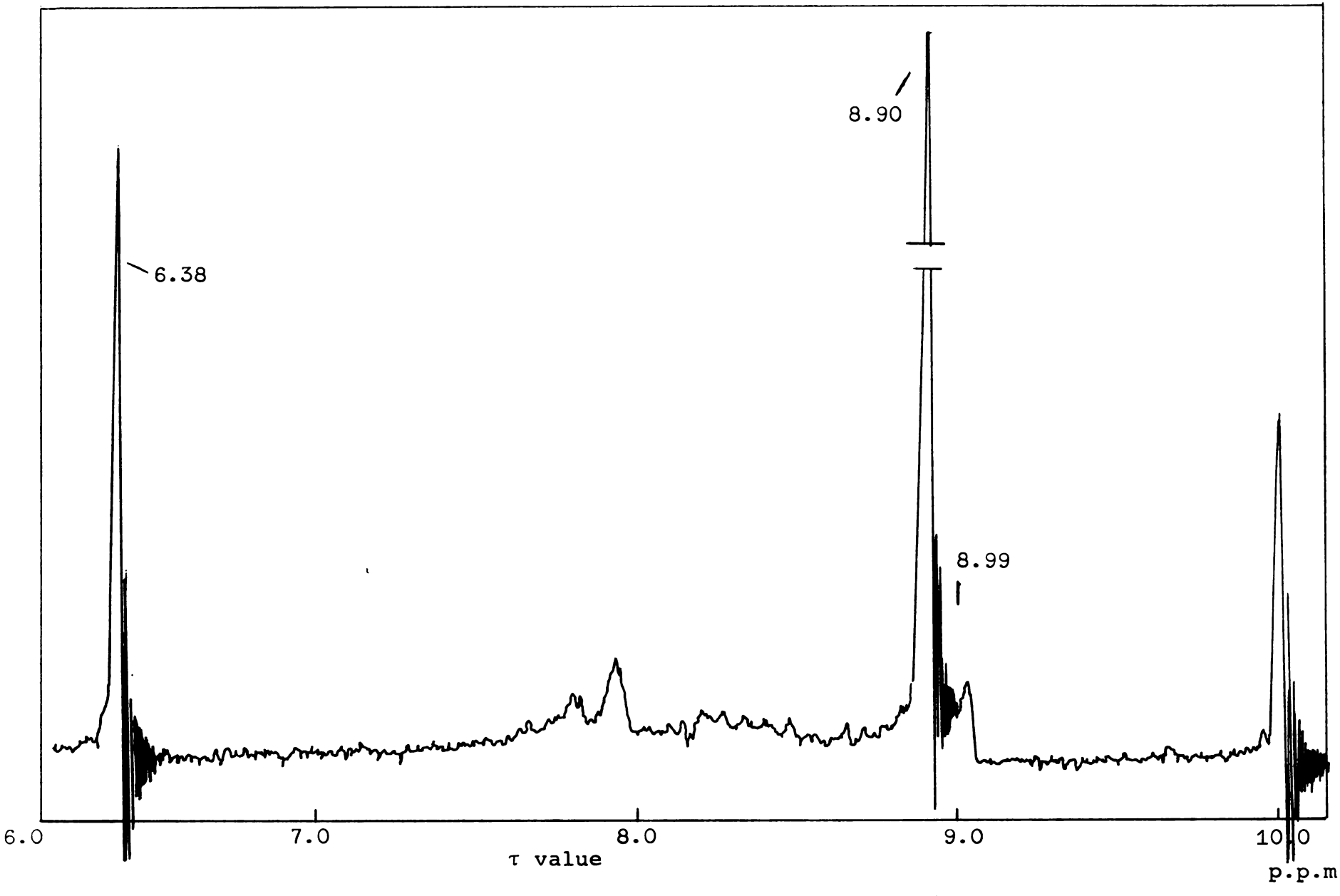


Fig. 5. N.M.R. spectrum of methyl trans,trans-puleganolate (LXVIIA).

identified as cis, trans-puleganolide (LXVIIIA). The infrared and n.m.r. spectra of the LXVIIIA isolated here were identical with those reported by Wolinsky (77).

5. Conversion of methyl trans,trans-puleganolate to cis,trans-puleganolide. A solution of LXVIIA (65 mg) in 3 ml. methanol containing 1 ml. conc. hydrochloric acid was refluxed for 5 hours and worked up by the previous procedure. The oil thus obtained (52 mg) was analyzed by v.p.c. and proved to be a mixture of LXVIA (27%), LXVIIIA (30%), unreacted LXVIIA (22%) and an unidentified component (22%) exhibiting absorption at 1730 cm^{-1} in the infrared. This compound may be a γ,δ-unsaturated isomer of LXVIA.

B. Direct Conversion of Pulegone Oxide LXIII to cis,trans-puleganolide

A solution of LXIII (100 mg) and sodium methoxide (145 mg) in glyme (10 ml.) was refluxed 19 hours followed by a work-up procedure similar to that used above. The acidic product (75 mg.) was dissolved in 2 ml. methanol containing 0.8 ml. conc. hydrochloric acid, and this solution was refluxed 1 hour followed by the usual work-up. The resulting oil (52 mg.) was analyzed by v.p.c. and infrared spectroscopy and proved to be 90% LXVIIIA.

Favorskii Reaction of Pulegone Oxide LXIV

A solution of LXIV (600 mg, 3.19 mmoles) and sodium methoxide (870 mg) in glyme (69 ml.) was refluxed for 19 hours and subjected to the same work-up procedure employed with

isomer **LXIII**. The neutral product (41 mg) showed three components on v.p.c. analysis, and infrared spectra of these disclosed no carbonyl absorption. Analysis of the acidic product mixture (501 mg), after methylation with diazomethane, demonstrated the presence of five components: **LXV** (15%), an equimolar mixture of **LXVIA** and **LXVIB** which was not resolved by the v.p.c. technique used here (23%), **LXVIIB** (33%), **LXVIIIA** (22%) and an unidentified component (8%). The proof for these structures rested on spectroscopic and chemical correlations.

A. Isolation and Structure Proof of Products

1. Methyl cis- and trans-pulegenates. The mixture of **LXVIA** and **LXVIB** exhibited an infrared spectrum consistent with a mixture of methyl cis- and trans-methylpulegenates. The n.m.r. spectrum showed a pair of doublets at τ 9.03 and 8.98 (J= 6.5 c.p.s.) (area 3.2), a broad singlet at τ 8.37 (area 6.1), a pair of singlets centered at τ 6.41 and separated by 1 c.p.s. (area 3), and a broad absorption from τ 8.3 to 6.7.

2. Methyl trans,cis-puleganolate. The infrared spectrum of **LXVIIB** showed hydroxyl absorption at 3500 cm^{-1} and carbonyl absorption at 1730 cm^{-1} (see Fig. 6). The n.m.r. spectrum exhibited a doublet at τ 9.12 (J= 6.5 c.p.s.) (area 3), a singlet at τ 8.98 (area 6), a singlet at τ 6.37 (area 3), and broad absorption from τ 8.4 to 7.1 (see Fig. 7).

3. Cis,trans-puleganolide. The infrared and n.m.r. spectra of **LXVIIIA** from this reaction were identical to corresponding spectra of authentic cis,trans-puleganolide (77).

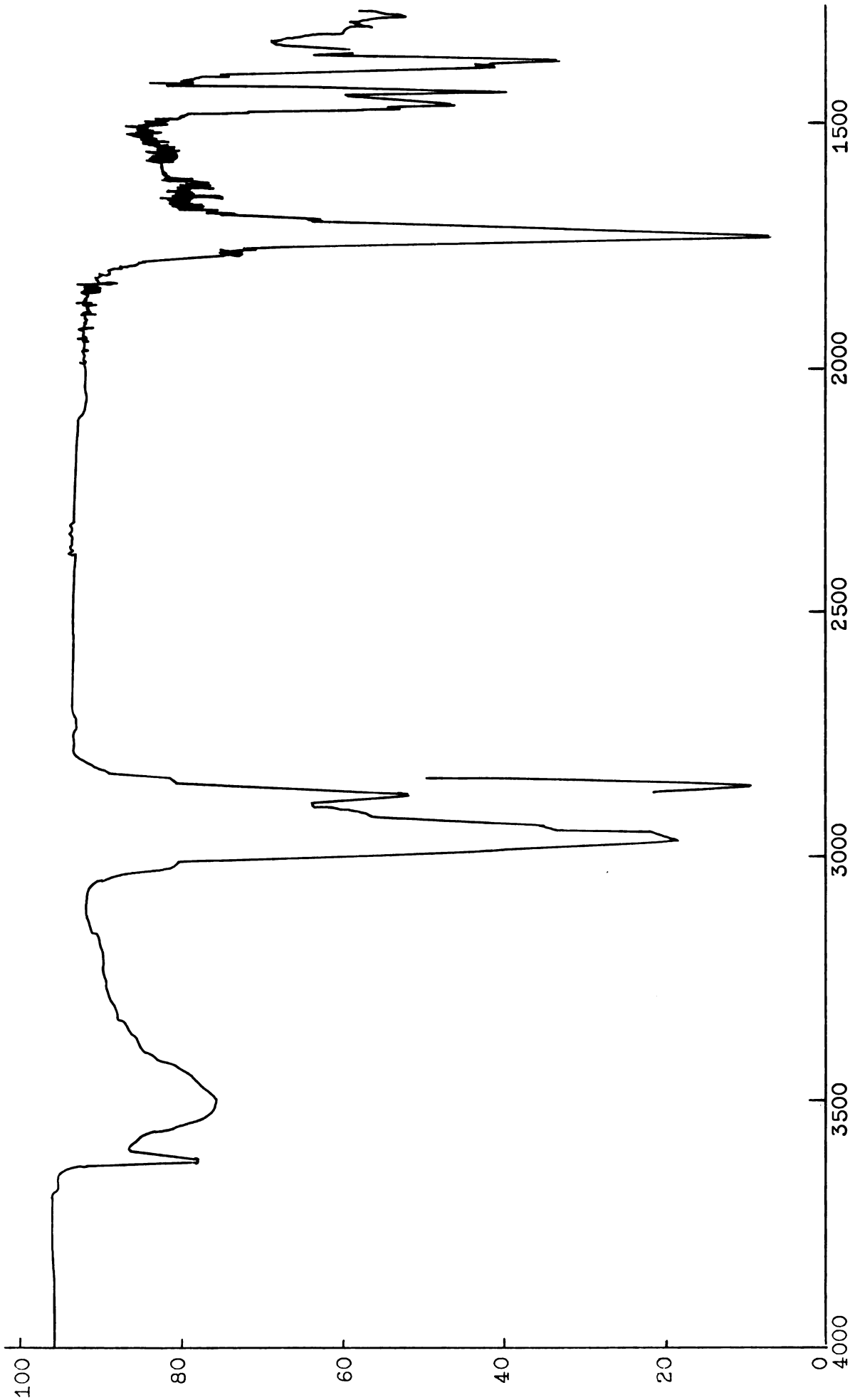


Fig. 6a. Infrared spectrum of methyl trans,cis-puleganolate (LXVIIB) in CCl_4.

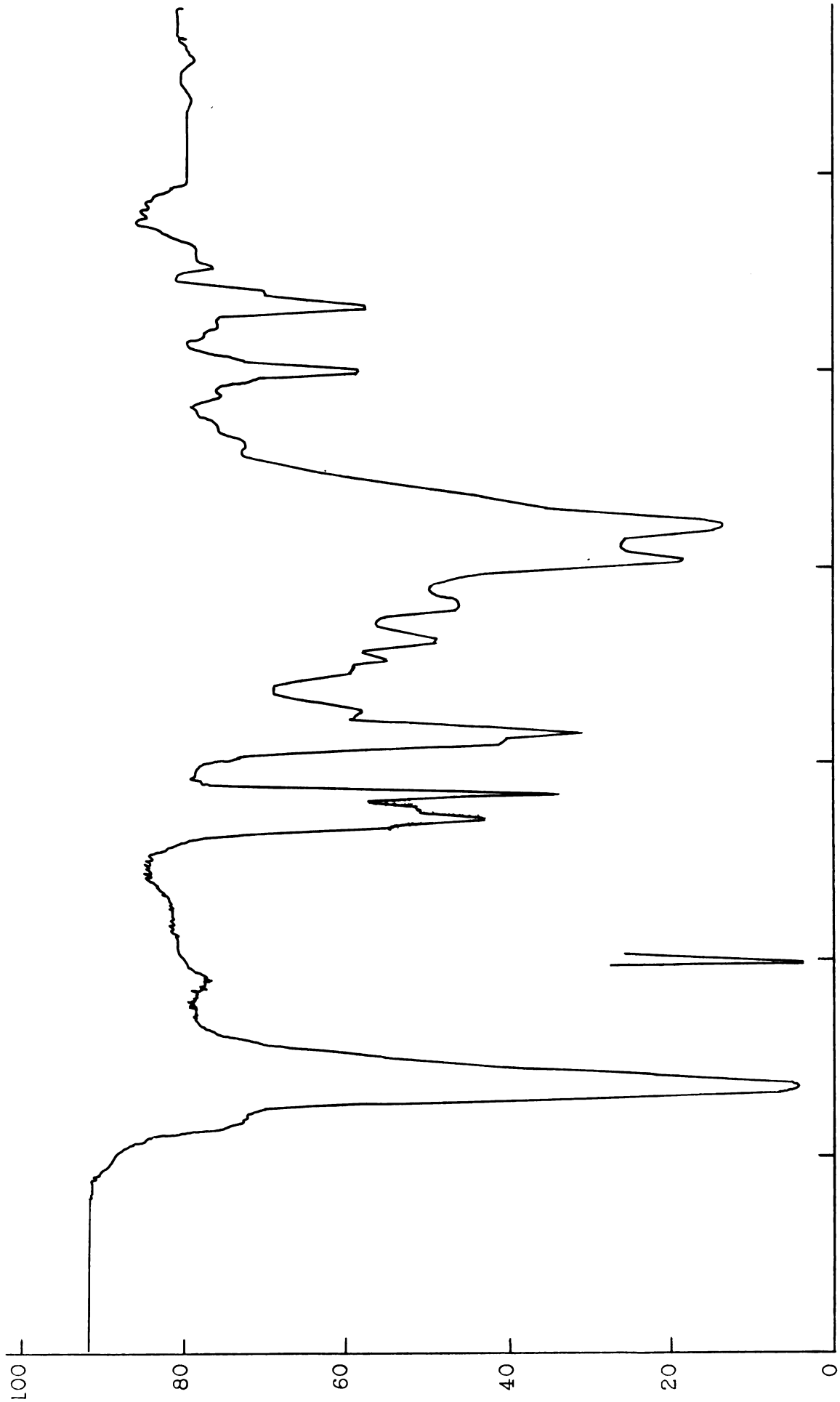


Fig. 6b. Infrared spectrum of methyl trans,cis-puleganolate (LXVIIB) in CCl_4.

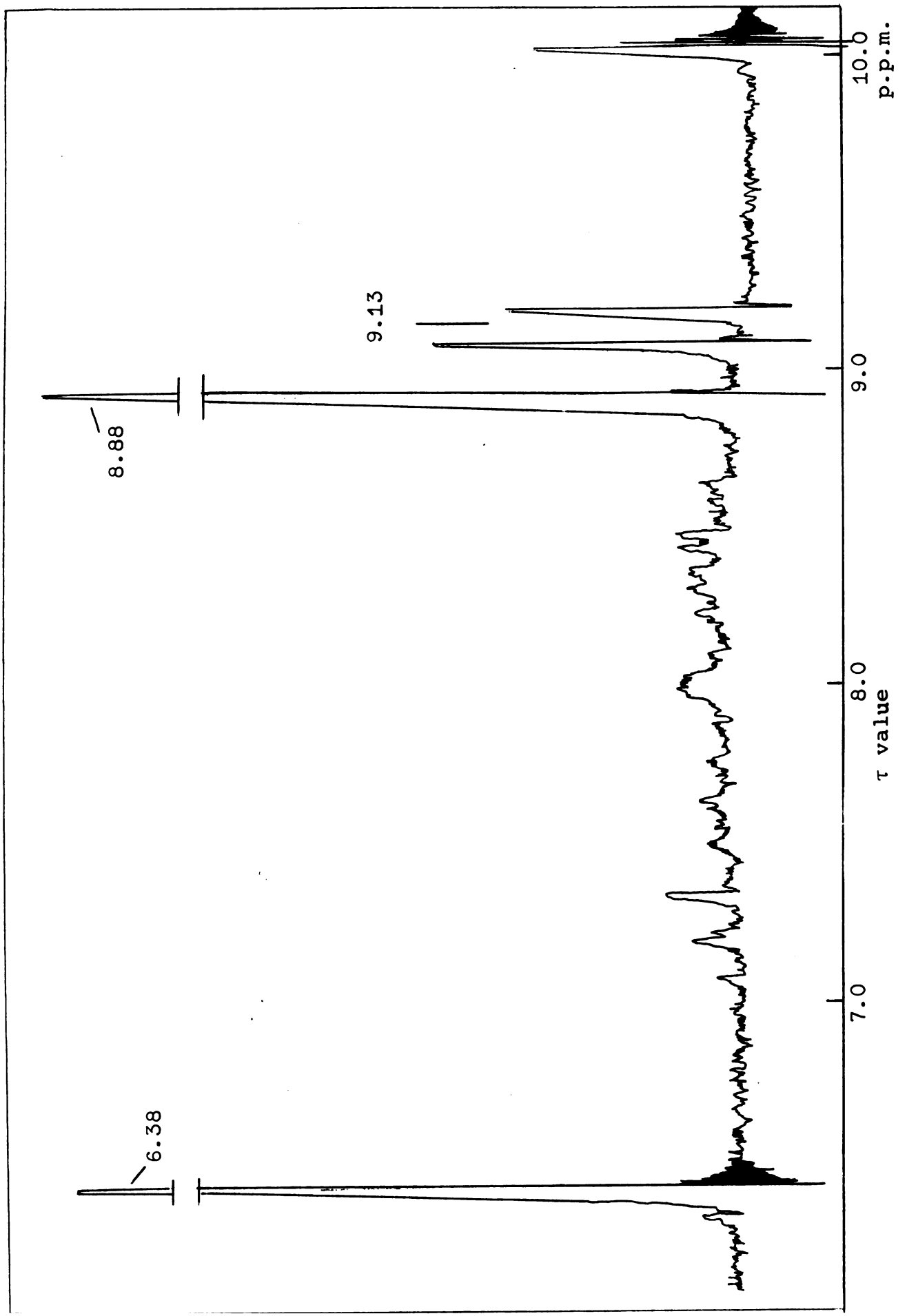


Fig. 7. N.M.R. spectrum of methyl trans,cis-puleganolate (LXVIIB).

4. Conversion of methyl cis- and trans-pulegenates to cis,trans- and cis,cis-puleganolide. A 50 mg. sample of the LXVIA plus LXVIB mixture was dissolved in 2 ml. methanol containing 0.8 ml. conc. hydrochloric acid and refluxed for 5 hours. The usual work-up gave 20 mg. of an oil which v.p.c. analysis showed to consist of at least four components. These were identified as starting material (21%), LXVIIIA (40%), LXVIIIB (33%) and an unidentified material (6%). The stereoisomeric puleganolides LXVIIIA and LXVIIIB were characterized by v.p.c. retention times and infrared spectra.

5. Conversion of methyl trans,cis-puleganolate to methyl cis-pulegenate and cis,cis-puleganolide. A solution of 48 mg. LXVIIB in 3 ml. methanol containing 1 ml. conc. hydrochloric acid was refluxed for 5 hours and subjected to the usual work-up procedure. At least three components were disclosed by v.p.c. analysis of the crude product (37 mg.). The first to be eluted (32%) was identified as LXVIB by comparison with authentic methyl cis-pulegenate (77). The next component (15%) was not identified. The major component (53%) proved to be LXVIIIB by comparison of its infrared spectrum with that of authentic cis,cis-puleganolide (77).

B. Direct Conversion of Pulegone Oxide LXIV to cis, trans- and cis,cis-puleganolide

A solution of LXIV (600 mg.) and sodium methoxide (870 mg.) in 60 ml. glyme was refluxed for 1 hour and worked up by the procedure used for the previous Favorskii reactions.

The neutral product (219 mg.) was analyzed by v.p.c. and proved to be largely (90%) recovered **LXIV**. The remaining neutral material was homogeneous to v.p.c. and exhibited an infrared spectrum similar to that found for a mixture of **LXVIA** and **LXVIB**.

The acidic product (283 mg.) was treated with diazomethane and analyzed by v.p.c. The major products were **LXV** (19%), **LXVIA** plus **LXVIB** (30%), **LXVIIB** (20%) and **LXVIIIA** (21%). Identification was based on v.p.c. retention times and infrared spectra.

Treatment of Methyl Trans,cis-puleganolate with Base

A 47 mg. sample of **LXVIIB** was mixed with 20 ml. of 10% sodium hydroxide solution, heated with vigorous stirring to 60°, and allowed to stand for 14 hours. Acidification to pH < 1 followed by ether extraction yielded 39 mg. of crude product. This was treated with diazomethane and analyzed by v.p.c. and infrared spectroscopy. Only recovered **LXVIIB** was observed.

Treatment of Cis,trans- and Cis,cis-puleganolide with Base

A solution of **LXVIIIA** (50 mg.) **LXVIIIB** (15 mg.) and sodium methoxide (87 mg.) in 6 ml. glyme was refluxed for 19 hours. A work-up similar to that used previously gave 48 mg. of crude material (both neutral and acidic) which was treated with diazomethane (no apparent reaction) and analyzed by v.p.c. Only recovered starting material was detected.

Deuterium Exchange of Pulegone Oxide

A mixture of 1.0 g **LXIII** in 5 ml cyclohexane (reagent grade) and 0.30 g anhydrous potassium carbonate in 5 ml deuterium oxide was refluxed with stirring for 72 hours. The mixture was taken up in ether, washed twice with 5% sodium hydroxide, twice with water, dried, and evaporated. The white crystalline product (710 mg) was recrystallized from pentane, giving 589 mg of needles, m. 57-8°. The infrared spectrum showed C-D stretch at 2100 and 2215 cm^{-1}. In the mass spectrum, **LXIII** displayed a parent peak at m/e=168 (relative intensity = 1.00) and P+1 and P+2 peaks of relative intensities 0.118 and 0.010, respectively. Corresponding peaks from the deuterated product showed relative intensities of 2.5, 13.5, 57.5, 9.0, and 1.0, for m/e 168 through 172, respectively. Calculations indicate 3.4% undeuterated product, 17.9% d_1, 75.7% d_2, and 3.1% d_3. The intensity of the peaks at τ 7.58 and τ 7.43 in the n.m.r. was decreased to ca. 10% of that in undeuterated **LXIII**.

An identical procedure, using 1.00 g **LXIV**, gave 423 mg colorless needles, m. 54-5°. Infrared analysis showed C-D stretch at 2215 and 2090 cm^{-1}. In the mass spectrum, **LXIV** displayed a parent peak at 168 (relative intensity = 1.00), and P+1 and P+2 peaks of relative intensities 0.12 and 0.10, respectively. Corresponding peaks of the deuterated product showed m/e 168 through 172 peaks with relative intensities of 5.5, 18.0, 62.0, 8.0, and 1.0, respectively. Values of 6.6%

undeuterated, 20.8% d_1, 71.9% d_2, and 0.7% d_3 product were obtained. The intensity of the peak at τ 7.68 in the n.m.r. was decreased to ca. 30% of that in undeuterated **LXIV**.

Conversion of Cholest-5-en-3β,4β-diol 3β-Tosylate (XCII) to Cholest-5-en-4α-ol(XCIII)

To a solution of 38.2 g **XCII** (0.069 mole) in 300 ml reagent benzene and 300 ml absolute ether was added 4.0 g lithium aluminum hydride (0.105 mole). After stirring at room temperature for 24 hours, the mixture was cooled, and ethyl acetate was added, followed by water. The mixture was filtered and the residue was washed with ether. The organic layer was washed with water, saturated sodium chloride solution, dried, decolorized, and evaporated. The residue was recrystallized from hexane and then from methanol-chloroform, giving 16.9 g **XCIII** (64% of theoretical), m. 123-5° (lit. (78): m. 143-4° from acetone-hexane).

Oxidation of Cholest-5-en-4α-ol to Cholest-5-en-4-one (XCIV)

The oxidation of **XCIII** was carried out using aluminum isopropoxide and cyclohexanone, following a procedure adapted from the oxidation of cholesterol (79). A 15% yield of **XCIV** was obtained, m. 112°, $\nu_{max}^{CCl_4}$ 1685, 1627 cm^{-1}.

Conversion of Cholest-5-en-4-one to 5β,6β-Epoxycholestan-4-one (LXXXIX)

Treatment of **XCIV** with sodium hydroxide and hydrogen peroxide in methanol according to the procedure of R. LeMahieu (51) gave **LXXXIX** in 65% yield, m. 105-6° (lit.: m. 98-100° (51),

102-4° (78). The spectral properties were: $\nu_{max}^{CCl_4}$ 1711 cm^{-1}; $\lambda_{max}^{cyclohexane}$ 304 mμ(ε 44.5); O.R.D. in 95% EtOH (c, 0.077), $[\Phi]_{325}$ +1925°, $[\Phi]_{306}$ ±0°, $[\Phi]_{280}$ -1935°; O.R.D. in cyclohexane (c,0.079), $[\Phi]_{337}$ +2220°, $[\Phi]_{316}$ ±0°, $[\Phi]_{295}$ -2020°; C.D. in 95 EtOH (c, 0.077), $[\Phi]_{307}$ +2650 (R_0= 2.02 x 10^{-40} c.g.s.)(see Fig. 8); C.D. in cyclohexane (c, 0.079), $[\Phi]_{318}$ +2780 (R_0= 2.31 x 10^{-40}).

Conversion of Cholest-5-en-4α-ol to 5α,6α-Epoxycholestan-4-one (LXXXVIII)

A solution of 6.8 g XCIII (17.6 mmole) and 4.9 g 85% m-chloroperbenzoic acid (30 mmoles) in 275 ml thiophene-free benzene was stirred at room temperature for 19 hours. A 10% sodium sulfite solution was added until a negative test with sodium iodide-starch paper was attained. The benzene layer was extracted with 5% sodium hydroxide solution, washed with water and saturated sodium chloride solution, dried and the benzene was evaporated. The residue was a gum which dould not be crystallized.

Seven g chromium trioxide (70 mmole) was added in small portions to 120 ml cold, well-stirred pyridine. Then the crude product from above in 25 ml pyridine was added in one portion and the mixture was stirred at room temperature for 5 days. After addition of ethyl acetate and filtration, as much pyridine as possible was evaporated at reduced pressure. The residue was taken up in ether and washed with 5% hydrochloric acid, water, saturated sodium chloride solution, dried,

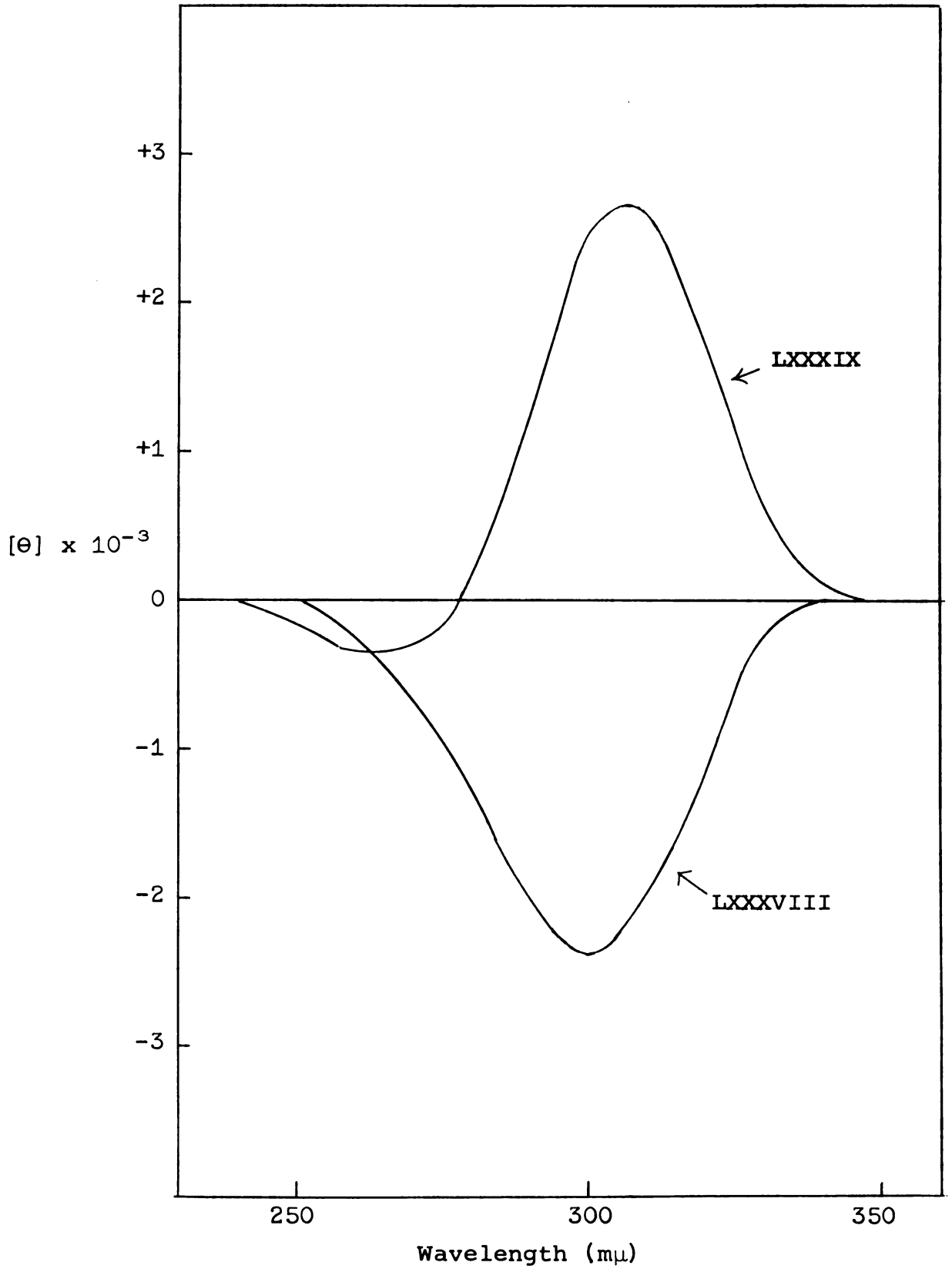


Fig. 8. C.D. spectra of 5α,6α-epoxycholestan-4-one (**LXXXVIII**) and 5β,6β-epoxycholestan-4-one (**LXXXIX**) in 95% EtOH.

decolorized, and the ether evaporated, leaving a green oil. Chromatography on 70 gm silica gel and elution with 1:7 chloroform:benzene gave 1.4 g of a non-recrystallizable solid. This material was purified by preparative thin layer chromatography using a 1 mm layer of silica gel PF_{254} (Brinkmann Instruments, Inc.), and eluting with chloroform. The band of Rf = 0.17-0.49 was recovered and recrystallized twice from methanol, yielding 500 mg **LXXXVIII**, m. 84-6° (lit. (78): 86-7°). The spectral properties were: $\nu_{max}^{CCl_4}$ 1725 cm^{-1}; $\lambda_{max}^{cyclohexane}$ 297 mμ(ε 37.7); O.R.D. in 95% EtOH (c, 0.058), $[\Phi]_{328}$ -1748°, $[\Phi]_{321}$ -1870°, $[\Phi]_{303}$ ±0°, $[\Phi]_{279}$ +1665°; O.R.D. in cyclohexane (c, 0.073), $[\Phi]_{329}$ -1900°, $[\Phi]_{324}$ -1620°, $[\Phi]_{319}$ -1860°, $[\Phi]_{311}$ -725°, $[\Phi]_{305}$ ±0°, $[\Phi]_{281}$ +1618°; C.D. in 95% EtOH (c,0.058), $[\Phi]_{300}$ -2360 (R_0= -2.38 x 10^{-40}c.g.s.) (see Fig. 8); C.D. in cyclohexane (c, 0.073), $[\Phi]_{324}$ -1160, $[\Phi]_{313}$ -2310, $[\Phi]_{310}$ -2240, $[\Phi]_{304}$ -2,640, $[\Phi]_{296-8}$ -2,340 (R_0= -253 x 10^{-40} c.g.s.).

4β,5β-Epoxycholestan-3-one (LXXXVI)

LXXXVI, prepared by the method of Shaw and Stevenson (80) exhibited the following spectral properties: $\nu_{max}^{CCl_4}$ 1710 cm^{-1}; $\lambda_{max}^{cyclohexane}$ 304 mμ(ε 32.1) and 313 mμ (ε 31.7); O.R.D. in 95% EtOH (c, 0.081), $[\Phi]_{328}$ +8920°, $[\Phi]_{307}$ ±0°, $[\Phi]_{282}$ -8080°; O.R.D. in cyclohexane (c, 0.081), $[\Phi]_{342}$ +9100°, $[\Phi[_{336}$ +7720°, $[\Phi]_{329}$ +9300°, $[\Phi]_{318}$ +3715°, $[\Phi]_{313}$ ±0°, $[\Phi]_{280}$ -8080°; C.D. in 95% EtOH (c, 0.081), $[\Phi]_{306}$ +12,400 (R_0= 12.5 x 10^{-40}c.g.s.); C.D. in cyclohexane (c, 0.081),

$[\phi]_{334}$ +4680, $[\phi]_{323}$ +10,200, $[\phi]_{321}$ +9950, $[\phi]_{313}$ +12,100, $[\phi]_{304}$ +10,470 (R_o= 11.6 x 10^{-40} c.g.s.).

LITERATURE CITED

1. B. Tchoubar, Compt. Rend. 208, 1020 (1939).
2. R. Loftfield, J. Am. Chem. Soc. 72, 632 (1950); 73, 4707 (1951).
3. J. Aston and J. Newkirk, J. Am. Chem. Soc. 73, 3900 (1951).
4. J. Burr and M. Dewar, J. Chem. Soc., 1201 (1954).
5. A. Fort, J. Am. Chem. Soc. 84, 2620 (1962).
6. G. Stork and I. Borowitz, J. Am. Chem. Soc. 82, 4307 (1960).
7. H. House and W. Gilmore, J. Am. Chem. Soc. 83, 3980 (1961).
8. B. Tchoubar, A. Gaudemer, J. Parello, and A. Skrobek, Bull. Soc. Chem. Fr., 2405 (1963).
9. F. Winternitz, C. Shoppee, D. Evans, and A. dePaulet, J. Chem. Soc., 1451 (1957).
10. N. Pappas and H. Nace, J. Am. Chem. Soc. 81, 4556 (1959).
11. A. Rowland, J. Org. Chem. 27, 1135 (1962).
12. P. Diassi and R. Palmore, J. Org. Chem. 26, 5240 (1961).
13. J. Cox, J. Chem. Soc., 4508 (1960).
14. H. House and H. Thompson, J. Org. Chem. 28, 164 (1963).
15. H. House and G. Frank, J. Org. Chem. 30, 2948 (1965).
16. E. Smissman, T. Lamke, and O. Kristiansen, J. Am. Chem. Soc. 88, 334 (1966).
17. J. Conia and J. Salann, Bull. Soc. Chim. Fr., 1957 (1964).
18. P. Eaton and T. Cole, J. Am. Chem. Soc. 86, 3158 (1964).
19. R. Pettit, J. Barborak, and J. Watts, J. Am. Chem. Soc. 88, 1328 (1966).
20. C. Engel, J. Am. Chem. Soc. 78, 4727 (1956).

21. N. Wendler, R. Graber, and G. Hazen, Chem. and Ind., 847 (1956).

22. Ibid., Tet. 3, 144 (1958).

23. R. Deghenghi, G. Schilling, and G. Papieneau-Conture, Can. J. Chem. 44, 789 (1966).

24. A. Fort, J. Am. Chem. Soc. 84, 2625 (1962).

25. Ibid., 84, 4979 (1962).

26. N. Turro and W. Hammond, J. Am. Chem. Soc. 87, 3258 (1965).

27. Ibid., 88, 2880 (1966).

28. Ibid., 88, 3672 (1966).

29. A. Kende, "Organic Reactions," Wiley, New York, 1960, Vol. 11, p. 261.

30. R. Breslow, L. Altman, A. Krebs, E. Mohacsi, I. Murata, R. Peterson, and J. Posner, J. Am. Chem. Soc. 87, 1326 (1965).

31. R. Breslow, T. Eicher, A. Krebs, R. Peterson, and J. Posner, J. Am. Chem. Soc. 87, 1320 (1965).

32. R. Breslow, J. Posner, and A. Krebs, J. Am. Chem. Soc. 85, 234 (1963).

33. R. Woodward and A. Clifford, J. Am. Chem. Soc. 63, 2727 (1941).

34. G. Hess and F. Urbanek, Ber. 91, 2733 (1958).

35. W. Ziegenbein, Ber. 94, 2989 (1961).

36. C. Rappe, Acta Chem. Scand. 17, 2766 (1963).

37. J. Kennedy, N. McCorkindale, R. Raphael, W. Scott, B. Zwanenburg, Proc. Chem. Soc., 148 (1964).

38. J. Romo and R. deVivar, J. Am. Chem. Soc. 79, 1118 (1957).

39. C. Rappe and G. Carlsson, Arkiv Kemi. 24, 105 (1965).

40. C. Rappe, Arkiv Kemi. 24, 95 (1965).

41. C. Rappe, Arkiv Kemi. 24, 315 (1965).

42. C. Rappe, Acta Chem. Scand. 20, 862 (1966).

43. E. Dehmlow, Z. Naturforsch, Pt. B, 20, 1128 (1965).

44. C. Rappe and K. Andersson, Arkiv Kemi. 24, 303 (1965).

45. W. Treibs, Ber. 64, 2178 (1931).

46. Ibid., 65, 163 (1932).

47. Ibid., 66, 610 (1933).

48. Ibid., 66, 1483 (1933).

49. H. House and F. Gilmore, J. Am. Chem. Soc. 83, 3972 (1961).

50. J. McGhie, P. Palmer, M. Rosenberger, J. Birchenough, and J. Cavalla, Chem. and Ind., 1221 (1959).

51. R. LeMahieu, Ph. D. Thesis, Michigan State University, 1963.

52. W. Reusch and R. LeMahieu, J. Am. Chem. Soc. 85, 1669 (1963).

53. G. Cavill and S. Achmad, Aust. J. Chem. 16, 858 (1963).

54. J. Wolinsky, H. Wolf, and T. Gibson, J. Org. Chem. 28, 274 (1963).

55. J. Wolinsky and D. Cahn, J. Org. Chem. 30, 41 (1965).

56. W. Reusch and C. Johnson, J. Org. Chem. 28, 2557 (1963).

57. G. Cavill and C. Hall, Personal Communication.

58. N. Kundu, S. Mukherjee, and P. Dutta, Tet. Letters, 627 (1962).

59. D. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, 1965, p. 144.

60. A. Nickon, J. Lambert, R. Williams, N. Werstiuk, J. Am. Chem. Soc. 88, 3354 (1966).

61. C. DePuy, F. Breitbeil, and K. DeBruin, J. Am. Chem. Soc. 88, 3347 (1966).

62. P. Wharton and T. Bair, J. Org. Chem. 31, 2480 (1966).

63. D. Cram, F. Hauck, K. Kopecky, and W. Nielson, J. Am. Chem. Soc. 81, 5767 (1959).

64. J. Wolinsky and D. Cahn, J. Org. Chem. 30, 41 (1965).

65. J. Katsuhara, J. Org. Chem., in press.

66. C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, Tetrahedron 21, 163 (1965).

67. M. Ligrand, R. Viennet, and J. Coumartin, Compt. rend 253, 2378 (1961).

68a. C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, 1960, p. 165.

68b. Ibid., p. 178.

69. K. Wellman, R. Records, E. Bunnenberg, and C. Djerassi, J. Am. Chem. Soc. 86, 492 (1964).

70. D. Williams and N. Bacca, Tetrahedron 21, 2021 (1965).

71. J. Connolly and R. McCrindle, Chem. and Ind., 379 (1965).

72. J. Ronayne and D. Williams, Chem. Comm., 712 (1966).

73. N.M.R. measurements were made by Dr. Lois Durham and her staff, Dept. of Chemistry, Stanford University, Stanford, California.

74. Low temperature C. D. measurements were made by Mrs. Ruth Records through the courtesy of Prof. Carl Djerassi, Dept. of Chemistry, Stanford University, Stanford, California.

75. K. Wellman, P. Laur, W. Briggs, A. Moscowitz, and C. Djerassi, J. Am. Chem. Soc. 87, 66 (1965).

76. E. Eliel, M. Gianni, T. Williams, and J. Stothers, Tet. Letters, 741 (1962).

77. Kindly provided by Prof. J. Wolinsky.

78. D. Lavie, Y. Kashman, and E. Glatter, Tetrahedron 22, 1103 (1966).

79. "Organic Syntheses," Coll. Vol. IV, Wiley, New York, 1963, p. 192.

80. J. Shaw and R. Stevenson, J. Chem. Soc. 3549 (1955).